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(54) CONJUGATES COMPRISED OF POLYMER AND HIV GP41-DERIVED PEPTIDES AND THEIR USE IN THERAPY

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Publication Classification

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(52) U.S. Cl. 530/350; 525/54.1

(57) ABSTRACT

Provided are conjugates comprising a polymer having operably bound thereto no less than two molecules of synthetic peptide derived from HIV gp41; methods of using these conjugates to inhibit transmission of HIV to a target cell by adding an amount of effective to inhibit infection of the cell by the virus; and methods of producing the conjugates by operably binding each molecule of synthetic peptide, via a reactive functionality, to the polymer.

10/671,282

1-9 19-30 WD

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Original) A conjugate comprising a polymer to which is operably bound no less than two molecules of synthetic peptides, wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a heptad repeat region of Human Immunodeficiency Virus (HIV) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the conjugate has durability comprising antiviral activity against HIV strains resistant to synthetic peptide alone.

2. (Original) The conjugate according to claim 1, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

3. (Original) The conjugate according to claim 2, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

4. (Original) The conjugate according to claim 1, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the HR1 region of HIV gp41.

5. (Original) The conjugate according to claim 4, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence.

6. (Original) The conjugate according to claim 1, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the HR2 region of HIV gp41.

7. (Original) The conjugate according to claim 6, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence.

8. (Original) The conjugate according to claim 1, wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the HR1 region of HIV gp41, and wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the HR2 region of HIV gp41.

9. (Original) The conjugate according to claim 1, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

Claims 10-18 (Cancelled)

19. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a ~~an amount of~~ conjugate according to claim 1 in an amount effective to inhibit infection of the cell by the virus~~; wherein the conjugate comprises a polymer to which is operably bound no less than two molecules of synthetic peptides, wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a heptad repeat region of Human Immunodeficiency Virus (HIV) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the conjugate has durability comprising antiviral activity against HIV strains resistant to synthetic peptide alone~~.

20. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a conjugate according to claim 2 in an amount effective to inhibit infection of the cell by the virus~~ The method according to claim 19, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons~~.

21. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a conjugate according to claim 3 in an amount effective to inhibit infection of the cell by the virus~~The method according to claim 20, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units~~.

22. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a conjugate according to claim 4 in an amount effective to inhibit infection of the cell by the virus~~The method according to claim 19, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the HR1 region of HIV gp41~~.

23. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a conjugate according to claim 5 in an amount effective to inhibit infection of the cell by the virus~~The method according to claim 22, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence~~.

24. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a conjugate according to claim 6 in an amount effective to inhibit infection of the cell by the virus~~The method according to claim 19, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the HR2 region of HIV gp41~~.

25. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a conjugate according to claim 7 in an amount effective to inhibit infection of the cell by the virus~~The method according to claim 24, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence~~.

26. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a conjugate according to claim 8 in an amount effective to inhibit infection of the cell by the virus~~The method according to claim 19, wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the HR1 region of HIV gp41, and wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the HR2 region of HIV gp41~~.

27. (withdrawn--currently amended) A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell a conjugate according to claim 9 in an amount effective to inhibit infection of the cell by the virus~~The method according to claim 19, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine~~.

28. (original) The method according to claim 19, wherein the conjugate inhibits fusion between the virus and the target cell in inhibiting infection of the cell by the virus.

29. (original) The method according to claim 19, wherein the conjugate further comprises a pharmaceutically acceptable carrier.

30. (original) The method according to claim 29, wherein the conjugate is administered to an HIV- infected individual.

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Sep 2006 (20060928/PD)
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HIGHEST APPLICATION PUBLICATION NUMBER: US2006218687
CA INDEXING IS CURRENT THROUGH 28 Sep 2006 (20060928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Sep 2006 (20060928/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006

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=> e bray brian/in
E1            1     BRAY BRADLEY/IN
E2            3     BRAY BRANDON R/IN
E3            7 --> BRAY BRIAN/IN
E4            1     BRAY BRIAN D/IN
E5            5     BRAY BRIAN L/IN
E6            2     BRAY BRUCE G/IN
E7            1     BRAY BRYAN KENNETH/IN
E8            4     BRAY BURTON A/IN
E9            1     BRAY CARL R/IN
E10           1     BRAY CHAD B/IN
E11           1     BRAY CHARLES E/IN
E12           1     BRAY CHARLES W/IN

=> s e3-e5
              7 "BRAY BRIAN"/IN
              1 "BRAY BRIAN D"/IN
              5 "BRAY BRIAN L"/IN
L1           13 ("BRAY BRIAN"/IN OR "BRAY BRIAN D"/IN OR "BRAY BRIAN L"/IN)

=> s l1 and (HIV or human immunodeficiency virus)
          45383 HIV
         522505 HUMAN
          25660 IMMUNODEFICIENCY
         105701 VIRUS
          18282 HUMAN IMMUNODEFICIENCY VIRUS
                   (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L2            6 L1 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l2 and (conjugate? or HR1 or HR2 or heptad)
         153066 CONJUGATE?
            521 HR1
            432 HR2
            842 HEPTAD
L3            6 L2 AND (CONJUGATE? OR HR1 OR HR2 OR HEPTAD)

=> d l3,cbib,clm,1-6

L3   ANSWER 1 OF 6  USPATFULL on STN
2004:159410 Conjugates comprised of polymer and HIV gp41-derived peptides
    and their use in therapy.
    Bray, Brian, Graham, NC, UNITED STATES
    Kang, Myung-Chol, Chapel Hill, NC, UNITED STATES
    Tvermoes, Nicolai, Durham, NC, UNITED STATES
    Kinder, Daniel, Durham, NC, UNITED STATES
    Lackey, John William, Hillsborough, NC, UNITED STATES
    US 2004122214 A1 20040624
    APPLICATION: US 2003-671282  A1  20030924 (10)
    PRIORITY: US 2002-414439P  20020927 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A **conjugate** comprising a polymer to which is operably bound no less than two molecules of synthetic peptides, wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a **heptad** repeat region of **Human Immunodeficiency Virus** (**HIV**) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the **conjugate** has durability comprising antiviral activity against **HIV** strains resistant to synthetic peptide alone.

2. The **conjugate** according to claim 1, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

3. The **conjugate** according to claim 2, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

4. The **conjugate** according to claim 1, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41.

5. The **conjugate** according to claim 4, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

6. The **conjugate** according to claim 1, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

7. The **conjugate** according to claim 6, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

8. The **conjugate** according to claim 1, wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41, and wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

9. The **conjugate** according to claim 1, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

10. A method of making a **conjugate**, the method comprising the steps of: (a) reacting a first molecule of synthetic peptide with a polymer in forming an intermediate comprising a first intermediate, wherein the first molecule of synthetic peptide operably binds to a first reactive functionality of the polymer; and (b) reacting the intermediate comprising the first intermediate with a second molecule of synthetic peptide, wherein the second molecule of synthetic peptide operably binds to the intermediate comprising the first intermediate via a second reactive functionality of the polymer, in forming a **conjugate** comprised of a polymer to which is operably bound no less than two molecules of synthetic peptides; and wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a **heptad** repeat region of **Human Immunodeficiency Virus** (**HIV**) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the **conjugate** has durability comprising antiviral

activity against **HIV** strains resistant to synthetic peptide alone.

11. The method according to claim 10, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

12. The method according to claim 11, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

13. The method according to claim 10, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41.

14. The method according to claim 13, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

15. The method according to claim 10, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

16. The method according to claim 15, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

17. The method according to claim 10, wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41, and wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

18. The method according to claim 10, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

19. A method of inhibiting transmission of **HIV** to a target cell, the method comprising adding to the virus and the cell an amount of **conjugate** effective to inhibit infection of the cell by the virus; wherein the **conjugate** comprises a polymer to which is operably bound no less than two molecules of synthetic peptides, wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a **heptad** repeat region of **Human Immunodeficiency Virus** (**HIV**) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the **conjugate** has durability comprising antiviral activity against **HIV** strains resistant to synthetic peptide alone.

20. The method according to claim 19, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

21. The method according to claim 20, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

22. The method according to claim 19, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41.

23. The method according to claim 22, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

24. The method according to claim 19, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

25. The method according to claim 24, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

26. The method according to claim 19, wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41, and wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

27. The method according to claim 19, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

28. The method according to claim 19, wherein the **conjugate** inhibits fusion between the virus and the target cell in inhibiting infection of the cell by the virus.

29. The method according to claim 19, wherein the **conjugate** further comprises a pharmaceutically acceptable carrier.

30. The method according to claim 29, wherein the **conjugate** is administered to an **HIV**-infected individual.

L3 ANSWER 2 OF 6 USPATFULL on STN
2004:83181 Pharmaceutical composition for improved administration of **HIV** gp41-derived peptides, and its use in therapy.
Heilman, David, Hillsborough, NC, UNITED STATES
Di, Jie, Chapel Hill, NC, UNITED STATES
Bray, Brian, Graham, NC, UNITED STATES
US 2004063637 A1 20040401
APPLICATION: US 2003-663589 A1 20030916 (10)
PRIORITY: US 2002-414441P 20020927 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A pharmaceutical composition comprised of a solution comprising synthetic peptide in admixture with a polyol; wherein the synthetic peptide is an **HIV** fusion inhibitor; wherein the synthetic peptide is in a final concentration in the pharmaceutical composition of not less than 70 mg/ml and not more than 500 mg/ml; and wherein the polyol is in a final concentration of no less than 5 weight % and no more than 75 weight % of the pharmaceutical composition.

2. The pharmaceutical composition according to claim 1, wherein the synthetic peptide is in a final concentration in the pharmaceutical composition of not less than 100 mg/ml and not more than 250 mg/ml.

3. The pharmaceutical composition according to claim 1, wherein the polyol is in a final concentration of no less than 10 weight % and no more than 50 weight % of the pharmaceutical composition.

4. The pharmaceutical composition according to claim 1, wherein the polyol comprises polyethylene glycol.

5. The pharmaceutical composition according to claim 1, further comprising a pharmaceutically acceptable carrier additional to the

polyol.

6. A method of treating **HIV** infection (preferably, **HIV**-1 infection) comprising administering to an **HIV**-infected individual a pharmaceutical composition according to claim 1.

7. A pharmaceutical composition comprised of a solution comprising synthetic peptide in admixture with a polyol; wherein the synthetic peptide is an **HIV** fusion inhibitor; wherein the synthetic peptide is in a final concentration in the pharmaceutical composition of not less than 100 mg/ml and not more than 250 mg/ml; and wherein the polyol is in a final concentration of no less than 10 weight % and no more than 50 weight % of the pharmaceutical composition.

8. The pharmaceutical composition according to claim 7, wherein the polyol comprises polyethylene glycol.

9. The pharmaceutical composition according to claim 7, further comprising a pharmaceutically acceptable carrier additional to the polyol.

10. A method of treating **HIV** infection (preferably, **HIV**-1 infection) comprising administering to an **HIV**-infected individual a pharmaceutical composition according to claim 7.

11. A synthetic peptide-containing pharmaceutical composition as a unit dose, wherein the pharmaceutical composition comprises an aqueous formulation comprising: (a) a polyol present as a pharmaceutically acceptable carrier in an amount not less than 5 weight % and not more than 75 weight % of the pharmaceutical composition as a unit dose; and (b) synthetic peptide comprising an **HIV** fusion inhibitor in a final concentration of the pharmaceutical composition of not less than 70 mg/ml and not more than 500 mg/ml.

12. The synthetic peptide-containing pharmaceutical composition according to claim 11, wherein the synthetic peptide is in a final concentration in the pharmaceutical composition of not less than 100 mg/ml and not more than 250 mg/ml.

13. The synthetic peptide-containing pharmaceutical composition according to claim 11, wherein the polyol is in a final concentration of no less than 10 weight % and no more than 50 weight % of the pharmaceutical composition.

14. The synthetic peptide-containing pharmaceutical composition according to claim 11, wherein the polyol comprises polyethylene glycol.

15. The synthetic peptide-containing pharmaceutical composition according to claim 11, further comprising a pharmaceutically acceptable carrier additional to the polyol.

16. A method of treating **HIV** infection (preferably, **HIV**-1 infection) comprising administering to an **HIV**-infected individual a synthetic peptide-containing pharmaceutical composition according to claim 11.

17. A synthetic peptide-containing pharmaceutical composition as a unit dose, wherein the pharmaceutical composition comprises an aqueous formulation comprising: (a) a polyol present as a pharmaceutically acceptable carrier in an amount not less than 10 weight % and not more than 50% of the pharmaceutical composition as a unit dose; and (b) synthetic peptide comprising an **HIV** fusion inhibitor in a final concentration of the pharmaceutical composition of not less than 100

mg/ml and not more than 250 mg/ml.

18. The synthetic peptide-containing pharmaceutical composition according to claim 17, wherein the polyol comprises polyethylene glycol.

19. The synthetic peptide-containing pharmaceutical composition according to claim 17, further comprising a pharmaceutically acceptable carrier additional to the polyol.

20. A method of treating **HIV** infection (preferably, **HIV**-1 infection) comprising administering to an **HIV**-infected individual a synthetic peptide-containing pharmaceutical composition according to claim 17.

L3 ANSWER 3 OF 6 USPATFULL on STN
2003:181682 Methods and compositions for peptide synthesis.
Bray, Brian, Graham, NC, UNITED STATES
Andersen, Marc, Raleigh, NC, UNITED STATES
Friedrich, Paul Erickson, Apex, NC, UNITED STATES
Kang, Myung-Chol, Chapel Hill, NC, UNITED STATES
Trimeris, Inc. (U.S. corporation)
US 2003125516 A1 20030703
APPLICATION: US 2002-109748 A1 20020329 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for synthesizing a peptide of the formula: X-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-Z (SEQ ID NO: 1), comprising: (a) reacting a side-chain protected peptide of the formula: EQAQIQQEKNEYELQKLDKWASLWEWF-Z (SEQ ID NO: 6), wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: X-WQEWEQKITALL-COOH (SEQ ID NO: 2), to yield a side-chain protected peptide of the formula: X-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-Z (SEQ ID NO: 1); wherein X is a protecting group, an acetyl group or a macromolecular carrier group; and wherein Z is a protecting group, an amido group, or a macromolecular carrier group.

2. The method of claim 1, wherein X is a protecting group selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

3. The method of claim 1, wherein Z is a protecting group selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

4. The method of claim 1 wherein X is a macromolecular carrier group selected from the group consisting of lipid-fatty acid **conjugates**, polyethylene glycol and carbohydrates.

5. The method of claim 1 wherein Z is a macromolecular carrier group selected from the group consisting of lipid-fatty acid **conjugates**, polyethylene glycol and carbohydrates.

6. The method of claim 1 which further comprises deprotecting the side chains of the side-chain protected peptide of the formula: X-WQEWEQKITALLEQAQQEKNEYELQKLDKWASLWEWF-Z (SEQ ID NO: 1).

7. The method of claim 1 or 6 wherein X is an acetyl group.

8. The method of claim 7 wherein Z is an amido group.

9. The method of claim 1 or 6 wherein X is a protecting group and wherein the method further comprises the step of modifying X into an acetyl group.

10. The method of claim 9, wherein Z is an amido group.

11. The method of claim 1 wherein the side-chain protected peptide of the formula: X-WQEWEQKITALL-COOH (SEQ ID NO: 2) is synthesized by solid phase peptide synthesis.

12. The method of claim 4 wherein the side-chain protected peptide of the formula: EQAQIQQEKEYELQKLDKWASLWEWF-Z (SEQ ID NO: 6) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: QKLDKWASLWEWF-Z (SEQ ID NO: 5),wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: EQAQIQQEKNEYEL-COOH (SEQ ID NO: 3) to yield the side-chain protected peptide of the formula: EQAQIQQEKNEYELQKLDKWASLWEWF- Z (SEQ ID NO: 6)

13. The method of claim 12 wherein the side-chain protected peptide of the formula: QKLDKWASLWEWF-Z (SEQ ID NO: 5) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: QKLDKWASLWEW-COOH (SEQ ID NO: 4) with phenylalanine amide to yield the side-chain protected peptide of the formula: QKLDKWASLWEWF-Z (SEQ ID NO: 5)

14. The method of claim 12, wherein the side-chain protected peptide of the formula: EQAQIQQEKNEYEL-COOH (SEQ ID NO: 3) is synthesized by solid phase peptide synthesis.

15. The method of claim 13, wherein the side-chain protected peptide of the formula: QKLDKWASLWEW-COOH (SEQ ID NO: 4) is synthesized bu solid phase peptide synthesis.

16. A set of peptide fragments comprising a set selected from the group consisting of:

(a)	WQEWEQKITALL,	(SEQ ID NO:2)
	EQAQIQQEKNEYEL,	(SEQ ID NO:3)
	QKLDKWASLWEW;	(SEQ ID NO:4)
(b)	WQEWEQKITALL,	(SEQ ID NO:2)
	EQAQIQQEKNEYEL,	(SEQ ID NO;3)
	QKLDKWASLWEWF;	(SEQ ID NO:5)
(c)	WQEWEQKITALL,	(SEQ ID NO:2)
	EQAQIQQEKNEYELQKLDKWASLWEWF;	(SEQ ID NO:6)
(d)	WQEWEQKITALL,	(SEQ ID NO:2)
	EQAQIQQEKNEYELQKLDKWASLWEW;	(SEQ ID NO:8)
(e)	WQEWEQKITALLEQAQIIQQEKNEYEL,	(SEQ ID NO:7)
	QKLDKWASLWEW; and	(SEQ ID NO:4)
(f)	WQEWEQKITALLEQAQIIQQEKNEYEL,	(SEQ ID NO:7)

QKLDKWASLWEWF. (SEQ ID NO:5)

17. A set of peptide fragments according to claim 16, wherein one or more of the side chains of said peptide fragments is protected with a protecting group.

18. A set of peptide fragments according to claim 17, wherein said protecting group is selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

19. The set of peptide fragments of claim 16, wherein the set comprises:

WQEWEQKITALL, (SEQ ID NO:2)

EQAQIQQEKNEYEL, and (SEQ ID NO:3)

QKLDKWASLWEW. 9SEQ ID NO:4)

20. The set of peptide fragments of claim 16, wherein the set comprises:

WQEWEQKITALL, (SEQ ID NO:2)

EQAQIQQEKNEYEL, and (SEQ ID NO;3)

QKLDKWASLWEWF. (SEQ ID NO:5)

21. The set of peptide fragments of claim 16, wherein the set comprises:

WQEWEQKITALL, and (SEQ ID NO:2)

EQAQIQQEKNEYELQKLDKWASWEWF. (SEQ ID NO:6)

22. The set of peptide fragments of claim 16, wherein the set comprises:

WQEWEQKITALL, and (SEQ ID NO:2)

EQAQIQQEKNEYELQKLDKWASLWEW. (SEQ ID NO:8)

23. The set of peptide fragments of claim 16, wherein the set comprises:

WQEWEQKITALLEQAQIIQQEKNEYEL, and (SEQ ID NO:7)

QKLDKWASLWEW. (SEQ ID NO:4)

24. The set of peptide fragments of claim 16, wherein the set comprises:

WQEWEQKITALLEQAQIIQQEKNEYEL, and (SEQ ID NO:7)

QKLDKWASLWEWF. (SEQ ID NO:5)

25. A peptide selected from the group consisting of:

WQEWEQKITALL, (SEQ ID NO:2)

EQAQIQQEKNEYEL, (SEQ ID NO:3)

QKLDKWASLWEW, 9SEQ ID NO:4)

QKLDKWASLWEWF, (SEQ ID NO:5)

EQAQIQQEKNEYELQKLDKWASLWEWF, (SEQ ID NO:6)

WQEWEQKITALLEQAQIIQQEKNEYEL, and (SEQ ID NO:7)

EQAQIQQEKNEYELQKLDKWASLWEW. (SEQ ID NO:8)

26. A peptide according to claim 25, wherein one or more of the side chains of said peptide is protected with a protecting group.

27. A peptide according to claim 26, wherein said protecting group is selected from the group consisting of b 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

28. The peptide of claim 25, wherein the peptide is WQEWEQKITALL (SEQ ID NO: 2).

29. The peptide of claim 25, wherein the peptide is EQAQIQQEKNEYEL (SEQ ID NO: 3).

30. The peptide of claim 25, wherein the peptide is QKLDKWASLWEW 9SEQ ID NO: 4).

31. The peptide of claim 25, wherein the peptide is QKLDKWASLWEWF (SEQ ID NO: 5).

32. The peptide of claim 25, wherein the peptide is EQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO: 6).

33. The peptide of claim 25, wherein the peptide is WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO: 7).

34. The peptide of claim 25, wherein the peptide is EQAQIQQEKNEYELQKLDKWASLWEW (SEQ ID NO: 8).

L3 ANSWER 4 OF 6 USPATFULL on STN
2002:276181 Methods and composition for peptide synthesis.
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Kang, Myung-Chol, Chapel Hill, NC, United States
Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6469136 B1 20021022
APPLICATION: US 1999-349205 19990707 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A set of peptides, wherein the set comprises: (a) WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), QKLDKWASLWEW (SEQ ID NO:4); (b) WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), QKLDKWASLWEWF (SEQ ID NO:5); (c) WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO:6); (d) WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYELQKLDKWASLWEW (SEQ ID NO:8); (e) WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), QKLDKWASLWEW (SEQ ID NO:4); or (f) WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), QKLDKWASLWEWF (SEQ ID NO:5).

2. A set of peptides according to claim 1, wherein one or more side chains of at least one peptide is protected with a protecting group.

3. A set of peptides according to claim 2, wherein said protecting group is selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

4. The set of peptides of claim 1, wherein the set comprises: WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), and QKLDKWASLWEW (SEQ ID NO:4).

5. The set of peptides of claim 1, wherein the set comprises: WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), and QKLDKWASLWEWF (SEQ ID NO:5).

6. The set of peptides of claim 1, wherein the set comprises: WQEWEQKITALL (SEQ ID NO:2), and EQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO:6).

7. The set of peptides of claim 1, wherein the set comprises: WQEWEQKITALL (SEQ ID NO:2), and EQAQIQQEKNEYELQKLDKWASLWEW (SEQ ID NO:8).

8. The set of peptides of claim 1, wherein the set comprises: WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), and QKLDKWASLWEW (SEQ ID NO:4).

9. The set of peptides of claim 1, wherein the set comprises: WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), and QKLDKWASLWEWF (SEQ ID NO:5).

10. A peptide selected from the group consisting of: WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), QKLDKWASLWEW (SEQ ID NO:4), QKLDKWASLWEWF (SEQ ID NO:5), EQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO:6), WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), and EQAQIQQEKNEYELQKLDKWASLWEW (SEQ ID NO:8).

11. A peptide according to claim 10, wherein one or more side chains of said peptide is protected with a protecting group.

12. A peptide according to claim 11, wherein said protecting group is selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

13. The peptide of claim 10, wherein the peptide is WQEWEQKITALL (SEQ ID NO:2).

14. The peptide of claim 10, wherein the peptide is EQAQIQQEKNEYEL (SEQ ID NO:3).

15. The peptide of claim 10, wherein the peptide is QKLDKWASLWEW (SEQ ID NO:4).

16. The peptide of claim 10, wherein the peptide is QKLDKWASLWEWF (SEQ ID NO:5).

17. The peptide of claim 10, wherein the peptide is EQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO:6).

18. The peptide of claim 10, wherein the peptide is WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7).

19. The peptide of claim 10, wherein the peptide is

EQAQIQQEKNEYELQKLDKWASLWEW (SEQ ID NO:8).

20. A set of peptides selected from the group consisting of: (a) WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), QKLDKWASLWEW (SEQ ID NO:4); (b) WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), QKLDKWASLWEWF (SEQ ID NO:5); (c) WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO:6); (d) WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYELQKLDKWASLWEW (SEQ ID NO:8); (e) WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), QKLDKWASLWEW (SEQ ID NO:4); and (f) WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), QKLDKWASLWEWF (SEQ ID NO:5).

21. A set of peptides according to claim 20, wherein one or more side chains of at least one peptide is protected with a protecting group.

22. A set of peptides according to claim 21, wherein said protecting group is selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

23. The set of peptides of claim 20, consisting of: WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), and QKLDKWASLWEW (SEQ ID NO:4).

24. The set of peptides of claim 20, consisting of: WQEWEQKITALL (SEQ ID NO:2), EQAQIQQEKNEYEL (SEQ ID NO:3), and QKLDKWASLWEWF (SEQ ID NO:5).

25. The set of peptides of claim 20, consisting of: WQEWEQKITALL (SEQ ID NO:2), and EQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO:6).

26. The set of peptides of claim 20, consisting of: WQEWEQKITALL (SEQ ID NO:2), and EQAQIQQEKNEYELQKLDKWASLWEW (SEQ ID NO:8).

27. The set of peptides of claim 20, consisting of: WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), and QKLDKWASLWEW (SEQ ID NO:4).

28. The set of peptides of claim 20, consisting of: WQEWEQKITALLEQAQIIQQEKNEYEL (SEQ ID NO:7), and QKLDKWASLWEWF (SEQ ID NO:5).

L3 ANSWER 5 OF 6 USPATFULL on STN
2001:142464 Methods and compositions for peptide synthesis.
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Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6281331 B1 20010828
APPLICATION: US 1998-45920 19980323 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A set of peptide fragments comprising a set selected from the group consisting of: (a) YTSLIHSLIEESQNQQ (SEQ ID NO:4), EKNEQELLELDKWASLWNWF (SEQ ID NO:12); (b) YTSLIHSLIEESQNQQ (SEQ ID NO:4), EKNEQELLEL (SEQ ID NO:11), DKWASLWNWF (SEQ ID NO:18); (c) YTSLIHSLIEESQNQQ (SEQ ID NO:4), EKNEQELLEL (SEQ ID NO:11), DKWASLWNW (SEQ ID NO:17); (d) YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQELLELDKWASLWNWF (SEQ ID NO:12); (e) YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQELLEL (SEQ ID NO:11), DKWASLWNWF (SEQ ID NO:18); (f) YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQELLEL (SEQ ID NO:11), DKWASLWNW (SEQ ID NO:17); (g)

YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQELLELDKWASLWNWF (SEQ ID NO:12); (h) YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQELLEL (SEQ ID NO:11), DKWASLWNWF (SEQ ID NO:18); (i) YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQELLEL (SEQ ID NO:11), DKWASLWNW (SEQ ID NO:17); (j) YTSLIHSLIEESQNQQ (SEQ ID NO:4), EKNEQEL (SEQ ID NO:10), LELDKWASLWNWF (SEQ ID NO:16); (k) YTSLIHSLIEESQNQQ (SEQ ID NO:4), EKNEQEL (SEQ ID NO:10), LELDKWASLWNW (SEQ ID NO:15); (l) YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQEL (SEQ ID NO:10), LELDKWASLWNWF (SEQ ID NO:16); (m) YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQEL (SEQ ID NO:10), LELDKWASLWNW (SEQ ID NO:15); (n) YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQEL (SEQ ID NO:10), LELDKWASLWNWF (SEQ ID NO:16); (o) YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQEL (SEQ ID NO:10), LELDKWASLWNW (SEQ ID NO:15), (p) YTSLIHSLIEESQNQ (SEQ ID NO:3), QEKNEQELLELDKWASLWNW (SEQ ID NO:8); (q) YTSLIHSLIEESQNQ (SEQ ID NO:3), QEKNEQELLELDKWASLWNWF (SEQ ID NO:9); (r) YTSLIHSLIEESQNQQEK (SEQ ID NO:5), NEQELLELDKWASLWNWF (SEQ ID NO:14); (s) YTSLIHSLIEESQNQQEK (SEQ ID NO:5), NEQELLELDKWASLWNW (SEQ ID NO:13); and (t) YTSLIHSLIEESQNQQ (SEQ ID NO:4), EKNEQELLELDKWASLWNW (SEQ ID NO:19).

2. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLIEESQNQQ (SEQ ID NO:4) and EKNEQELLELDKWASLWNWF (SEQ ID NO:12).

3. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLEEESQNQQ (SEQ ID NO:4), EKNEQELLEL (SEQ ID NO:11), and DKWASLWNWF (SEQ ID NO:18).

4. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLEEESQNQQ (SEQ ID NO:4), EKNEQELLEL (SEQ ID NO:11), and DKWASLWNW (SEQ ID NO:17).

5. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), and EKNEQELLELDKWASLWNWF (SEQ ID NO:12).

6. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQELLEL (SEQ ID NO:11), and DKWASLWNWF (SEQ ID NO:18).

7. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQELLEL (SEQ ID NO:11), and DKWASLWNW (SEQ ID NO:17).

8. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), and EKNEQELLELDKWASLWNWF (SEQ ID NO:12).

9. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQELLEL (SEQ ID NO:11), and DKWASLWNWF (SEQ ID NO:18).

10. The set of peptide fragments of claim 1, wherein the set comprises: (i) YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQELLEL (SEQ ID NO:11), and DKWASLWNW (SEQ ID NO:17).

11. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLIEESQNQQ (SEQ ID NO:4), EKNEQEL (SEQ ID NO:10), and LELDKWASLWNWF (SEQ ID NO:16).

12. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLIEESQNQQ (SEQ ID NO:4), EKNEQEL (SEQ ID NO:10), and LELDKWASLWNW (SEQ ID NO:15).

13. The set of peptide fragments of claim 1, wherein the set comprises: (1) YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQEL (SEQ ID NO:10), and LELDKWASLWNWF (SEQ ID NO:16).

14. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), EKNEQEL (SEQ ID NO:10), and LELDKWASLWNW (SEQ ID NO:15).

15. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQEL (SEQ ID NO:10), and LELDKWASLWNWF (SEQ ID NO:16).

16. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSL (SEQ ID NO:2), IEESQNQQ (SEQ ID NO:7), EKNEQEL (SEQ ID NO:10), and LELDKWASLWNW (SEQ ID NO:15).

17. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLIEESQNQ (SEQ ID NO:3), and QEKNEQELLELDKWASLWNW (SEQ NO:8).

18. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLIEESQNQ (SEQ ID NO:3), and QEKNEQELLELDKWASLWNWF (S ID NO:9).

19. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLEEESQNQQEK (SEQ ID NO:5), and NEQELLELDKWASLWNWF (SEQ ID NO:14).

20. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLIEESQNQQEK (SEQ ID NO:5), and NEQELLELDKWASLWNW (SEQ ID NO:3).

21. The set of peptide fragments of claim 1, wherein the set comprises: YTSLIHSLIEESQNQQ (SEQ ID NO:4), and EKNEQELLELDKWASLWNW (SEQ ID NO:19).

22. A peptide selected from the group consisting of: YTSLIHSL (SEQ ID NO:2), IEESQNQ (SEQ ID NO:6), IEESQNQQ (SEQ ID NO:7), QEKNEQELLELDKWASLWNW (SEQ ID NO:8), EKNEQEL (SEQ ID NO:10), EKNEQELLEL (SEQ ID NO:11), NEQELLELDKWASLWNW (SEQ ID NO:13), LELDKWASLWNW (SEQ ID NO:15), LELDKWASLWNWF (SEQ ID NO:16), DKWASLWNW (SEQ ID NO:17), DKWASLWNWF (SEQ ID NO:18), and EKNEQELLELDKWASLWNW (SEQ ID NO:19).

23. The peptide of claim 22, wherein the peptide is YTSLIHSL (SEQ ID NO:2).

24. The peptide of claim 22, wherein the peptide is IEESQNQ (SEQ ID NO:6).

25. The peptide of claim 22, wherein the peptide is IEESQNQQ (SEQ ID NO:7).

26. The peptide of claim 22, wherein the peptide is QEKNEQELLELDKWASLWNW (SEQ ID NO:8).

27. The peptide of claim 22, wherein the peptide is EKNEQEL (SEQ ID NO:10).

28. The peptide of claim 22, wherein the peptide is EKNEQELLEL (SEQ ID NO:11).

29. The peptide of claim 22, wherein the peptide is NEQELLELDKWASLWNW (SEQ ID NO;13).

30. The peptide of claim 22, wherein the peptide is LELDKWASLWNW (SEQ ID NO:15).

31. The peptide of claim 22, wherein the peptide is LELDKWASLWNWF (SEQ ID NO:16).

32. The peptide of claim 22, wherein the peptide is DKWASLWNW (SEQ ID NO:17).

33. The peptide of claim 22, wherein the peptide is DKWASLWNWF (SEQ ID NO:18).

34. The peptide of claim 22, wherein the peptide is EKNEQELLELDKWASLWNW (SEQ ID NO:19).

L3 ANSWER 6 OF 6 USPATFULL on STN
2000:7382 Methods and compositions for peptide synthesis.
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Merutka, Gene, Hillsborough, NC, United States
Trimeris, Inc., United States (U.S. corporation)
US 6015881 20000118
APPLICATION: US 1998-71877 19980501 (9)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for the synthesis of a peptide having the formula Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2 (SEQ ID NO: 1), comprising: (a) reacting a side-chain protected peptide of the formula: Fmoc-EKNEQELLEL-COOH (SEQ ID NO:11) with a side chain-protected peptide of the formula: NH2 -DKWASLWNWF-NH2 (SEQ ID NO: 18) to yield a side-chain protected peptide of the formula: Fmoc-EKNEQELLELDKWASLWNWF-NH2 (SEQ ID NO: 12); (b) deprotecting the amino terminus of the peptide produced in (a); (c) reacting the peptide produced in (b) with a side-chain protected peptide of the formula: Fmoc-YTSLIHSLIEESQNQQ-COOH (SEQ ID NO:4) to yield a side-chain protected peptide of the formula: Fmoc-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2 (SEQ ID NO: 1); (d) modifying the amino terminus of the peptide produced in (c) into an acetyl modification; and (e) deprotecting the side chains of the side-chain protected peptide of (d) to yield a peptide of the formula: Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2 (SEQ ID NO: 1). 2.

2. A method for the synthesis of a peptide having the formula Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2 (SEQ ID NO: 1), comprising: (a) reacting a side-chain protected peptide of the formula: Fmoc-EKNEQELLEL-COOH (SEQ ID NO:11) with a side chain-protected peptide of the formula: NH2 -DKWASLWNWF-NH2 (SEQ ID NO: 18) to yield a side-chain protected peptide of the formula: Fmoc-EKNEQELLELDKWASLWNWF-NH2 (SEQ ID NO: 12); (b) deprotecting the amino terminus of the peptide produced in (a); (c) reacting the peptide produced in (b) with a side-chain protected peptide of the formula: Ac-YTSLIHSLIEESQNQQ-COOH (SEQ ID NO:4) to yield a side-chain protected peptide of the formula: Ac-YTSLIHSLIEESQNQQEENEQELLELDKWASLWNWF-NH2 (SEQ ID NO: 1); and (d) deprotecting the side chains of the side-chain protected peptide of (c) to yield a peptide of the formula: Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2 (SEQ ID NO: 1). 3.

3. A method for the synthesis of a peptide of the formula:

X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1), comprising: (a) reacting a side-chain protected peptide of the formula: EKNEQELLELDKWASLWNWF-Z (SEQ ID NO:12), wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQ-COOH (SEQ ID NO:4), to yield a side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); wherein X is a protecting group, an acetyl group or a macromolecular carrier group selected from the group consisting of lipid fatty acid **conjugates**, polyethylene glycol and carbohydrates; and wherein Z is a protecting group, an amido group, or a macromolecular carrier group selected from the group consisting of lipid fatty acid **conjugates**, polyethylene glycol and carbohydrates.

4. The method of claim 3, wherein X is a protecting group selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

5. The method of claim 3, wherein Z is a protecting group selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

6. The method of claim 3 which further comprises deprotecting the side chains of the side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO: 1).

7. The method of claim 3 or 6 wherein X is an acetyl group.

8. The method of claim 7 wherein Z is an amido group.

9. The method of claim 3 or 6 wherein X is a protecting group and wherein the method further comprises the step of modifying X into an acetyl group.

10. The method of claim 9, wherein Z is an amido group.

11. The method of claim 3 wherein the side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQ-COOH (SEQ ID NO: 4) is synthesized by a method comprising: (a) reacting a side-chain protected peptide of the formula: IEESQNQQ-OPNB (SEQ ID NO:7), wherein OPNB represents a para-nitro benzyl ester group, and wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: X-YTSLIHSL-COOH (SEQ ID NO:4) (b) deprotecting the carboxy terminus of the peptide produced in (a) to yield the side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQ-COOH (SEQ ID NO:4).

12. The method of claim 11 wherein the carboxy terminus of the peptide produced in (a) is deprotected by palladium-catalyzed hydrogenolysis.

13. The method of claim 11 wherein the side-chain protected peptide of the formula: IEESQNQQ-OPNB (SEQ ID NO:7) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: IEESQNQ-COOH (SEQ ID NO:6) with the para-nitro benzyl ester of glutamine (HGlnOPNB), to yield the side-chain protected peptide of the formula: IEESQNQQ-OPNB (SEQ ID NO:7).

14. The method of claim 3, wherein the side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQ-COOH
(SEQ ID NO:4), is synthesized by solid phase peptide synthesis.

15. The method of claim 3 wherein the side-chain protected peptide of the formula: EKNEQELLELDKWASLWNWF-Z
(SEQ ID NO:12) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: DKWASLWNW-Z
(SEQ ID NO:18), wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: EKNEQELLEL-COOH
(SEQ ID NO:11) to yield the side-chain protected peptide of the formula: EKNEQELLELDKWASLWNW-Z (SEQ ID NO:12).

16. The method of claim 15 wherein the side-chain protected peptide of the formula: DKWASLWNWF-Z
(SEQ ID NO:18) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: DKWASLWNW-COOH
(SEQ ID NO:17) with phenylalanine amide to yield the side-chain protected peptide of the formula: DKWASLWNWF-Z
(SEQ ID NO:18).

17. The method of claim 3, wherein the side-chain protected peptide of the formula: EKNEQELLELDKWASLWNWF-Z
(SEQ ID NO:12) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: LELDKWASLWNWF-Z
(SEQ ID NO:16); wherein the amino terminus id deprotected with a side-chain protected peptide of the formula: AEKNEQEL-COOH
(SEQ ID NO:10) to yield a side-chain protected peptide of the formula: EKNEQELLELDKWASLWNWF-Z (SEQ ID NO:12).

18. The method of claim 17, wherein the side-chain protected peptide of the formula: LELDKWASLWNWF-Z
(SEQ ID NO:16) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: LELDKWASLWNW-COOH
(SEQ ID NO:15) with phenylalanine amide to yield a side-chain protected peptide of the formula: LELDKWASLWNWF-Z
(SEQ ID NO:16).

19. The method of claim 3 wherein the side-chain protected peptide of the formula: EKNEQELLELDKWASLWNWF-Z
(SEQ ID NO:12) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: EKNEQELLELDKWASLWNW-COOH
(SEQ ID NO:19) with phenylalanine amide, to yield a side-chain protected peptide of the formula: EKNEQELLELDKWASLWNWF-Z
(SEQ ID NO:12). 20.

20. A method of claim 19 wherein the side-chain protected peptide of the formula: EKNEQELLELDKWASLWNW-COOH (SEQ ID NO:19) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: DKWASLWNW-COOH
(SEQ ID NO:17), wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: EKNEQELLEL-COOH
(SEQ ID NO:11) to yield a side-chain protected peptide of the formula: EKNEQELLELDKWASLWNW-COOH (SEQ ID NO:19).

21. The method of claim 19, wherein the side-chain protected peptide of the formula: EKNEQELLELDKWASLWNW-COOH
(SEQ ID NO:19) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: LELDKWASLWNW-COOH

(SEQ ID NO:15), wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: EKNEQEL-COOH (SEQ ID NO:10), to yield a side-chain protected peptide of the formula: EKNEQELLELDKWASLWNW-COOH (SEQ ID NO:19).

22. The method of claim 7, wherein the side-chain protected peptide of the formula: Ac-YTSLIHSLIEESQNQQ-COOH (SEQ ID NO:4), is synthesized by a method comprising: (a) acetylating a side-chain protected peptide of the formula: YTSLIHSLIEESQNQQ-OPNB (SEQ ID NO:4), wherein OPNB represents a para-nitro benzyl ester group, and wherein the amino terminus is deprotected, to yield a side-chain protected peptide of the formula: Ac-YTSLIHSLIEESQNQQ-OPNB (SEQ ID NO:4); (b) deprotecting the carboxy terminus of the peptide produced in (a), to yield a side-chain protected peptide of the formula: Ac-YTSLIHSLIEESQNQQ-COOH (SEQ ID NO:4).

23. The method of claim 22, wherein said acetylating is accomplished by reacting the side-chain protected peptide of the formula: YTSLIHSLIEESQNQQ-OPNB (SEQ ID NO:4) with acetic anhydride.

24. The method of claim 22, wherein the side-chain protected peptide of the formula: YTSLIHSLIEESQNQQ-OPNB (SEQ ID NO:4) is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: IEESQNQQ-OPNB (SEQ ID NO:7), wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: YTSLIHSL-COOH (SEQ ID NO:2), to yield the side-chain protected peptide of the formula: YTSLIHSLIEESQNQQ-OPNB (SEQ ID NO:4).

25. A method for the synthesis of a peptide of the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1), comprising: (a) reacting a side-chain protected peptide of the formula: QEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:9), wherein the amino terminus deprotected; with a side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQ-COOH (SEQ ID NO:3), to yield a side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); wherein Z is a protecting group, an acetyl group or a macromolecular carrier group selected from the group consisting of lipid fatty acid **conjugates**, polyethylene glycol and carbohydrates; and Z is a protecting group, an amido group or a macromolecular carrier group selected from the group consisting of lipid fatty acid **conjugates**, polyethylene glycol and carbohydrates.

26. The method of claim 25 wherein X is a protecting group selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

27. The method of claim 25, wherein Z is a protecting group selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and a para-nitrobenzyl ester group.

28. The method of claim 25 which further comprises deprotecting the side chains of the side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1).

29. The method of claim 25 or 28 wherein X is an acetyl group.

30. The method of claim 29 wherein Z is an amido group.

31. The method of claim 25 or 28 wherein X is a protecting group and wherein the method further comprises the step of modifying X into an acetyl group.

32. The method of claim 31, wherein Z is an amido group.

33. The method of claim 25 wherein the side-chain protected peptide of the formula: QEKNEQELLELDKWASLWNWF-Z
(SEQ ID NO:9), is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: QEKNEQELLELDKWASLWNW-Z
(SEQ ID NO:8) with phenylalanine amide, to yield the side chain protected peptide of the formula: QEKNEQELLELDKWASLWNWF-Z
(SEQ ID NO:9).

34. The method of claim 25, wherein the side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQ-COOH
(SEQ ID NO:3) is synthesized by solid phase peptide synthesis.

35. A method for the synthesis of a peptide of the formula: XYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1), comprising: (a) reacting a side-chain protected peptide of the formula: NEQELLELDKWASLWNWF-Z (SEQ ID NO:14), wherein the amino terminus is deprotected; with a side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQEK-COOH
(SEQ ID NO:5), wherein R is a protecting group; to yield a side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); wherein X is a protecting group, an acetyl group, or a macromolecular carrier group selected from the group consisting of lipid fatty acid **conjugates**, polyethylene glycol and carbohydrates; and wherein Z is a protecting group, an amido group or a macromolecular carrier group selected from the group consisting of lipid fatty acid **conjugates**, polyethylene glycol and carbohydrates.

36. The method of claim 35, wherein X is a protecting group selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and para-nitrobenzyl ester group.

37. The method of claim 35, wherein Z is a protecting group selected from the group consisting of 9-fluoroenylmethoxy-carbonyl (Fmoc), t-butyl (t-Bu), trityl (trt), t-butyloxycarbonyl (Boc), carbobenzoxyl, dansyl and para-nitrobenzyl ester group.

38. The method of claim 35, which further comprises deprotecting the side chains of the side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1).

39. The method of claim 35 or 38 wherein X is an acetyl group.

40. The method of claim 39 wherein Z is an amido group.

41. The method of claim 35 or 38 wherein X is a protecting group and wherein the method further comprises the step of modifying X into an acetyl group.

42. The method of claim 41 wherein Z is an amido group.

43. The method of claim 35, wherein the side-chain protected peptide of the formula: NEQELLELDKWASLWNWF-Z (SEQ ID NO:14), is synthesized by a method comprising: reacting a side-chain protected peptide of the formula: NEQELLELDKWASLWNW-Z (SEQ ID NO:13) with phenylalanine amide, to yield the side-chain protected peptide of the formula: NEQELLELDKWASLWNWF-Z (SEQ ID NO:14).

44. The method of claim 35 wherein the side-chain protected peptide of the formula: X-YTSLIHSLIEESQNQQEK-COOH (SEQ ID NO: 5) is synthesized by solid phase peptide synthesis.

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=> e kang myung choi/in
E1            4      KANG MYOUNG HUN/IN
E2            4      KANG MYUNG AH/IN
E3            0 --> KANG MYUNG CHOI/IN
E4            5      KANG MYUNG CHOL/IN
E5            4      KANG MYUNG G/IN
E6            4      KANG MYUNG GOO/IN
E7            1      KANG MYUNG GYUN/IN
E8            5      KANG MYUNG HO/IN
E9            1      KANG MYUNG JI/IN
E10           1      KANG MYUNG JIN/IN
E11          15      KANG MYUNG KOO/IN
E12          16      KANG MYUNG SAM/IN

=> s e4
L4            5 "KANG MYUNG CHOL"/IN

=> d his

     (FILE 'HOME' ENTERED AT 05:19:18 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 05:19:28 ON 02 OCT 2006
                E BRAY BRIAN/IN
L1           13 S E3-E5
L2            6 S L1 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3            6 S L2 AND (CONJUGATE? OR HR1 OR HR2 OR HEPTAD)
                E KANG MYUNG CHOI/IN
L4            5 S E4

=> s l4 not l1
L5            0 L4 NOT L1

=> e tvermoes nicolai/in
E1            1      TVEREZY JURY F/IN
E2            3      TVERGYAK JOSEPH/IN
E3            1 --> TVERMOES NICOLAI/IN
E4            2      TVERMOES NICOLAI A/IN
E5            1      TVERRAN ALV/IN
E6            2      TVERSKAYA JULIA/IN
E7            2      TVERSKOI DAVID N/IN
E8            2      TVERSKOY BORIS S/IN
E9            1      TVERSKOY GRIGORY N/IN
E10           2      TVERSKY OREN J/IN
E11           3      TVERYANOVICH EDUARD V/IN
E12           1      TVESKOV BJARNE/IN

=> s e3-e4
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              1 "TVERMOES NICOLAI"/IN
              2 "TVERMOES NICOLAI A"/IN
L6            3 ("TVERMOES NICOLAI"/IN OR "TVERMOES NICOLAI A"/IN)

=> s l6 not l1
L7            2 L6 NOT L1

=> d l7,ti,1-2

L7   ANSWER 1 OF 2  USPATFULL on STN
TI     Benzimidazole compounds and antiviral uses thereof

L7   ANSWER 2 OF 2  USPATFULL on STN
TI     Benzimidazole compounds and antiviral uses thereof


=> d l7,cbib,clm,1-2

L7   ANSWER 1 OF 2  USPATFULL on STN
2006:167854 Benzimidazole compounds and antiviral uses thereof.
    Lackey, John William, Hillsborough, NC, UNITED STATES
    Kinder, Daniel S., Apex, NC, UNITED STATES
    Tvermoes, Nicolai A., Durham, NC, UNITED STATES
    Trimeris, Inc. (U.S. corporation)
    US 2006142365 A1 20060629
    APPLICATION: US 2006-346758  A1  20060202 (11)
    PRIORITY: US 2001-290038P  20010511 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A compound of the Formula I:    ##STR249## or a pharmaceutically-
       acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer,
       diastereomer, racemate or mixture of stereoisomer thereof, wherein:
       R1 and R2 are each independently: hydrogen, saturated or
       unsaturated straight or branched substituted or unsubstituted alkyl,
       substituted or unsubstituted cycloalkyl, substituted or unsubstituted
       heterocycloalkyl, substituted or unsubstituted heterocycloaryl;
       substituted or unsubstituted aryl, substituted or unsubstituted
       heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if
       present, the substituent is at least one alkanoyl, imide, alkyl,
       hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide,
       alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester,
       azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester,
       cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon,
       polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone,
       lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime,
       phosphate, phosphinate, phosphonate, phosphonic acid, quaternary
       ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester,
       sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;
       R3 is hydrogen, halide, saturated or unsaturated straight or
       branched substituted or unsubstituted alkyl, hydroxy, substituted or
       unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or
       unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl,
       or substituted or unsubstituted heteroaryl; wherein, if present the
       substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide,
       methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal,
       acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide,
       carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin,
       diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon,
       halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone,
       nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate,
       phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt,
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sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4' , R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; X is a bond, straight chain or branched substituted or unsubstituted alkyl, -(alkyl)N--, -(alkyl)O--, --C.dbd.N--, carbonyl, phosphorus, or sulfur; Y is nitrogen; n=1 is an integer from 0 to about 1; with the proviso that compounds of Formula I do not include a compound where R1, R2, R3, R4, R4', R8, R8' are hydrogen, X is a bond, and n=0; or a compound where R3, R4, R4', R8, and R8' are hydrogen, X is a bond, n=0, one of R1 or R2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

2-25. (canceled)

26. The compound according to claim 1 having Formula III: ##STR250## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, amide, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside,

glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester, cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

27. The compound according to claim 26, wherein: R1, and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12 alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

28. The compound according to claim 26, wherein: R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

29. The compound according to claim 26, wherein: R6 is a saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, C1-C4 alkoxy, substituted or unsubstituted C2-C6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C1-C4 alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

30. The compound according to claim 26, wherein: R1 and R2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl, hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl, 2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-thiophenyl)ethyl, N-benzyl-4-piperidinyl, 3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl,

cyclopentyl, or cyclohexyl.

31. The compound according to claim 26, wherein R6 is hydrogen.

32. The compound according to claim 26, wherein the compound of Formula III is an enantiomer or diastereomer.

33. The compound according to claim 26, wherein R4, R5', R8', and R9' are hydrogen.

34. The compound according to claim 26, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

35. The compound according to claim 26, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

36. The compound according to claim 26, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

37. The compound according to claim 26 having Formula XII: ##STR251##

38-63. (canceled)

64. A pharmaceutical composition comprising the compound according to claim 26 and a pharmaceutically acceptable carrier.

65-66. (canceled)

67. A method of treating, preventing, or ameliorating one or more symptoms associated with a respiratory syncytial virus (RSV) infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 26 and a pharmaceutically acceptable carrier.

68. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered orally, parenterally, transdermally, or mucosally.

69. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered in an amount from about 10 mg/kg/day to about 15 mg/kg/day.

70. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the mammal is a human subject.

71. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the human subject is a human infant.

72. A method of inhibiting membrane fusion associated events characteristic of a viral infection in a mammal comprising administering the compound of claim 26 and a pharmaceutically acceptable carrier.

73. A method of treating, preventing, or ameliorating one or more symptoms associated with a HPIV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 26 and a pharmaceutically acceptable carrier.

74. The compound of claim 26 which is a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, diastereomer, racemate or mixture of stereisomers.

L7 ANSWER 2 OF 2 USPATFULL on STN
2003:173906 Benzimidazole compounds and antiviral uses thereof.
Lackey, John William, Hillsborough, NC, UNITED STATES
Kinder, Daniel S., Apex, NC, UNITED STATES
Tvermoes, Nicolai A., Durham, NC, UNITED STATES
US 2003119754 A1 20030626
APPLICATION: US 2002-141839 A1 20020509 (10)
PRIORITY: US 2001-290038P 20010511 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound of the Formula I: ##STR247## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R1 and R2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group; R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate,

phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; X is a bond, straight chain or branched substituted or unsubstituted alkyl, -(alkyl)N--, -(alkyl)O--, --C.dbd.N--, carbonyl, phosphorus, or sulfur; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is an integer from 0 to about 4; with the proviso that compounds of Formula I do not include a compound where R1, R2, R3, R4, R4', R8, R8' are hydrogen, X is a bond, and n=0 or 1; or a compound where R3, R4, R4', R8, and R8' are hydrogen, X is a bond, n=0, one of R1 or R2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

2. The compound according to claim 1, wherein: R1 and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl group having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is least one C1-C4 alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or C1-C4 alkylamine; R3 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl C1-C8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent, is at least one hydroxy, fluoride, chloride, bromine, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, carboxylic acid, ester, amine, or C1-C4 alkylamine; R4, R4', R8, and R8' each independently is hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, carboxylic acid, ester, C1-C4 amide, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide; X is a bond, straight chain or branched substituted or unsubstituted C1-C4 alkyl, --(C1-C4 alkyl)N--, --(C1-C4 alkyl)O--, carbonyl, or sulfur; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is from 0 to about 1.

3. The compound according to claim 1, wherein: X is a bond, methylene, or ethylene; Y is nitrogen, phosphorus, oxygen, or sulfur, wherein, if Y is oxygen or sulfur, R2 is not present; and n is 1.

4. The compound according to claim 1, wherein: R3 is a substituted or unsubstituted phenyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted acridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted benzodioxanyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted phenylphenolyl, wherein, if present, the substituent is at least one C1-C4 alkyl, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, fluoride, chloride, or bromide; X is a methylene; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is 1.

5. The compound according to claim 1, wherein at least one of R1, R2, or R3is a benzimidazole.

6. The compound according to claim 5, wherein X is a bond or methylene, R3 is a 2-benzimidazole, and at least one of R1 or R2 is a 2-benzimidazole or 2-methylenebenzimidazole.

7. The compound according to claim 1, wherein the compound of Formula I is an enantiomer or diastereomer.

8. The compound according to claim 1, wherein R4' and R8' are hydrogen, methyl, methyl ester, ethyl ester, C1-C2 amide, carboxylic acid, methoxy, or sulfonamide.

9. The compound according to claim 1, wherein R4' and R8' are both hydrogen.

10. The compound according to claim 1, wherein R4, R4', R8, and R8' are all hydrogen.

11. The compound according to claim 1, wherein at least one of R4, R4', R8, or R8' is not hydrogen.

12. The compound according to claim 1, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

13. The compound according to claim 1, wherein at least three of R4, R4', R8, and R8' are not hydrogen.

14. The compound according to claim 1 having Formula VII: ##STR248##

15. The compound according to claim 1, wherein the compound is selected from the group consisting of: 1-(1H-Benzimidazol-2-ylmethyl)-2-morpholin-4-ylmethyl-1H-benzimidazole-5-carboxylic acid methyl ester; 1-(1H-Benzimidazol-2-ylmethyl)-2-morpholin-4-ylmethyl-1H-benzimidazole-6-carboxylic acid methyl ester; {1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidin-3-yl}-methanol; {1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidin-2-yl}-methanol; 2-{1-[1-(1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidin-2-yl}-ethanol; [1,2,4]Oxadiazol-3-ylmethyl-2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-1H-benzoimidazole; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-(3-trifluoromethyl-phenyl)piperazine; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-(4-trifluoromethyl-phenyl)piperazine; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-pyridin-2-ylpiperazine; (R)-{1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidin-2-yl}-methanol; (S)-1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid methyl ester; (S)-1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid amide; 2-{4-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperazin-1-yl}-acetamide; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidine-3-carboxylic acid 1 (1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl ester; and 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1 H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid 1-(1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl ester.

16. A compound of the Formula II: ##STR249## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen,

saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt,. sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R1 and R2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group; R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkyl, hydroxy, halide, methoxy, ethoxy, amine, cyano. alkanoyl, imide, amine, amide, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, halogen, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

17. The compound according to claim 16, wherein R1 and R2 are each independently: C1-C8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or alkylamine.

18. The compound according to claim 16, wherein R3 is

C1-C4 straight chain or branched alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, carboxylic acid, ester, amine, or C1-C4 alkylamine.

19. The compound according to claim 16, wherein R4, R4', R8, and R8' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

20. The compound according to claim 16, wherein at least one of R1, R2, or R3 is a benzimidazole.

21. The compound according to claim 16, wherein R3 is a 2-benzimidazole, and at least one of R1 or R2 is a 2-benzimidazole or 2-methylene benzimidazole.

22. The compound according to claim 16, wherein the compound of Formula II is an enantiomer or diastereomer.

23. The compound according to claim 16, wherein R4, R4', R8, and R8' are hydrogen.

24. The compound according to claim 16, wherein at least one of R4, R4', R8, or R8' is not hydrogen.

25. The compound according to claim 16 having Formulas VIII, IX, X, or XI: ##STR250##

26. A compound of the Formula III: ##STR251## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, amide, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or

unsubstituted heteroaryl, wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated,saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester, cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

27. The compound according to claim 26, wherein: R1, and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12 alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

28. The compound according to claim 26, wherein: R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

29. The compound according to claim 26, wherein: R6 is a saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, C1-C4 alkoxy, substituted or unsubstituted C2-C6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C1-C4 alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

30. The compound according to claim 26, wherein: R1 and R2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl,

hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl, 2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-thiophenyl)ethyl, N-benzyl-4-piperidinyl, 3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl, cyclopentyl, or cyclohexyl.

31. The compound according to claim 26, wherein R6 is hydrogen.

32. The compound according to claim 26, wherein the compound of Formula III is an enantiomer or diastereomer.

33. The compound according to claim 26, wherein R4', R5', R8', and R9' are hydrogen.

34. The compound according to claim 26, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

35. The compound according to claim 26, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

36. The compound according to claim 26, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

37. The compound according claim 26 having Formula XII: ##STR252##

38. A compound of the Formula IV: ##STR253## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: --R1--N--R2-- form a saturated or unsaturated substituted or unsubstituted heterocycloalkyl ring, substituted or unsubstituted heteroaryl ring, wherein, if present, the substituent is at least one substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkoxy, amides, sulfonamides, esters, hydroxy, halide, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, carbonyl, nitro, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R6, R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, or sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside,

glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, alkanoyl, imide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl.

39. The compound according to claim 38, wherein: --R1--N--R2-- form a saturated or unsaturated, substituted or unsubstituted 3 to 7 membered cycloalkyl, substituted or unsubstituted 3 to 7 membered heterocycloalkyl, substituted or unsubstituted 3 to 7 membered heteroaryl, wherein, if present, the substituent is at least one substituted or unsubstituted C1-C4 alkyl, substituted or unsubstituted C1-C4 alkoxy, C1-C4 esters, hydroxy, fluoride, chloride, bromide, substituted or unsubstituted 3 to 8 membered aryl, substituted or unsubstituted 4 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, carbonyl, or nitro.

40. The compound according to claim 38, wherein: R4, R4', R5, R5', R6, R8, R8', R9, and R9' are each independently hydrogen, C-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

41. The compound according to claim 38, wherein R4', R5', R8', and R9' are hydrogen.

42. The compound according to claim 38, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

43. The compound according to claim 38, wherein R5, R5', R9, and R9' are hydrogen.

44. The compound according to claim 38, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

45. The compound according to claim 38, wherein R6 is hydrogen.

46. The compound according to claim 38, wherein: --R1--N--R2-- form a 5, 6, or 8 membered ring; and R4, R4', R5, R5', R6, R8, R8', R9, and R9 are each independently are hydrogen C1-C2 alkyl, C1-C2 alkoxy, amine, C1-C2 alkylamine, fluoride, chloride, bromide,

hydroxy, nitro, C1-C2 sulfide, or C1-C2 sulfonyl.

47. The compound according to claim 38, wherein the 5, 6, or 8 membered ring formed by --R1--N--R2-- is a pyrrolidinyl, piperidinyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, piperazinyl, quinolinyl, acridinyl, thiazole, morpholinyl, or unsubstituted or substituted phenyl wherein, if present, the substituent, if present, is at least one methyl, ethyl, ester, methanol, 2-ethanol, or aldehyde.

48. The compound according to claim 38, wherein: --R1--N--R2-- form a cyclic structure: 2,5-dihydropyrrolyl, 3,5-dimethylpyrrolidinyl, 2-hydroxymethylpyrrolidinyl, 2-(2-hydroxyethyl)piperidinyl, N-carbaldehydepiperazinyl, N-(3-trifluoromethylphenyl)piperazinyl, N-(4-hydroxyphenyl)piperazinyl, N-(benzylcarbate)piperazinyl, tetrahydrothiazolyl, N-(4-acetylphenyl)piperazinyl, or cyclooctazanyl.

49. The compound according to claim 38, wherein the compound of Formula IV is an enantiomer or diastereomer.

50. The compound according to claim 38 having Formula XII: ##STR254##

51. The compound according to claim 38 having Formula XIV: ##STR255##

52. A compound of the Formula V: ##STR256## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, alkanoyl, imide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl. R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R7, R7', R8, R8', R9, R9', R10, and R10' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or

unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R_6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro amide, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and m is an integer from 0 to about 4.

53. The compound according to claim 52, wherein: R_1 is saturated or unsaturated straight or branched substituted or unsubstituted C_1-C_{11} alkyl, C_1-C_{12} alkoxy, substituted or unsubstituted C_1-C_{11} alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C_1-C_4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

54. The compound according to claim 52, wherein: R_3 is hydrogen, C_1-C_8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine.

55. The compound according to claim 52, wherein: R_4, R_4', R_5, R_5', R_7, R_7', R_8, R_8', R_9, R_9', R_{10}, and R_{10}' are each independently hydrogen,

methyl, methyl ester, ethyl ester, C1-C2 amide, carboxylic acid, methoxy, or sulfonamide; R6 is hydrogen or benzimidazole; and m is 1.

56. The compound according to claim 52, wherein R4', R5', R7', R8', R9', and R10' are hydrogen.

57. The compound according to claim 52, wherein R1 is hydrogen.

58. The compound according to claim 52, wherein at least one R4, R4', R8, and R8', are not hydrogen.

59. The compound according to claim 52, wherein at least two R5, R5', R9, and R9', are not hydrogen.

60. The compound according to claim 52, wherein at least one R7, R7', R10, and R10' are not hydrogen.

61. A compound of the formula: ##STR257##

62. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition comprising the compound according to claim 16 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising the compound according to claim 26 and a pharmaceutically acceptable carrier.

65. A pharmaceutical composition comprising the compound according to claim 38 and a pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising the compound according to claim 52 and a pharmaceutically acceptable carrier.

67. A method of treating, preventing, or ameliorating one or more symptoms associated with a respiratory syncytial virus (RSV) infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

68. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered orally, parenterally, transdermally, or mucosally.

69. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered in an amount from about 10 mg/kg/day to about 15 mg/kg/day.

70. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the mammal is a human subject.

71. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the human subject is a human infant.

72. A method of inhibiting membrane fusion associated events characteristic of a viral infection in a mammal comprising administering the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

73. A method of treating, preventing, or ameliorating one or more

symptoms associated with a HPIV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

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=> e kinder daniel/in
E1            2     KINDER CLAUDE E/IN
E2            2     KINDER DALE J/IN
E3            1 --> KINDER DANIEL/IN
E4            2     KINDER DANIEL S/IN
E5            2     KINDER DANIEL STUART/IN
E6            3     KINDER DAVID B/IN
E7            4     KINDER DAVID H/IN
E8            1     KINDER DAVID M/IN
E9            4     KINDER DENNIS G/IN
E10           1     KINDER FLORENCE E/IN
E11           5     KINDER FLOYD A/IN
E12           6     KINDER FREDERICK R JR/IN

=> s e3-e5
              1 "KINDER DANIEL"/IN
              2 "KINDER DANIEL S"/IN
              2 "KINDER DANIEL STUART"/IN
L8            5 ("KINDER DANIEL"/IN OR "KINDER DANIEL S"/IN OR "KINDER DANIEL
                STUART"/IN)

=> d his

     (FILE 'HOME' ENTERED AT 05:19:18 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 05:19:28 ON 02 OCT 2006
                E BRAY BRIAN/IN
L1           13 S E3-E5
L2            6 S L1 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3            6 S L2 AND (CONJUGATE? OR HR1 OR HR2 OR HEPTAD)
                E KANG MYUNG CHOI/IN
L4            5 S E4
L5            0 S L4 NOT L1
                E TVERMOES NICOLAI/IN
L6            3 S E3-E4
L7            2 S L6 NOT L1
                E KINDER DANIEL/IN
L8            5 S E3-E5

=> s l8 not l1
L9            4 L8 NOT L1

=> d l9,cbib,clm,1-4

L9   ANSWER 1 OF 4  USPATFULL on STN
2006:167854 Benzimidazole compounds and antiviral uses thereof.
    Lackey, John William, Hillsborough, NC, UNITED STATES
    Kinder, Daniel S., Apex, NC, UNITED STATES
    Tvermoes, Nicolai A., Durham, NC, UNITED STATES
    Trimeris, Inc. (U.S. corporation)
    US 2006142365 A1 20060629
    APPLICATION: US 2006-346758  A1  20060202 (11)
    PRIORITY: US 2001-290038P  20010511 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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CLM What is claimed is:

1. A compound of the Formula I: ##STR249## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; X is a bond, straight chain or branched substituted or unsubstituted alkyl, -(alkyl)N--, -(alkyl)O--, --C.dbd.N--, carbonyl, phosphorus, or sulfur; Y is nitrogen; n=1 is an integer from 0 to about 1; with the proviso that compounds of Formula I do not include a compound where R1, R2, R3, R4, R4', R8, R8' are hydrogen, X is a bond, and n=0; or a compound where R3, R4, R4', R8, and R8' are hydrogen, X is a bond, n=0, one of R1 or R2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

2-25. (canceled)

26. The compound according to claim 1 having Formula III: ##STR250## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, amide, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester, cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

27. The compound according to claim 26, wherein: R1, and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12 alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is

at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

28. The compound according to claim 26, wherein: R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

29. The compound according to claim 26, wherein: R6 is a saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, C1-C4 alkoxy, substituted or unsubstituted C2-C6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C1-C4 alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

30. The compound according to claim 26, wherein: R1 and R2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl, hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl, 2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-thiophenyl)ethyl, N-benzyl-4-piperidinyl, 3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl, cyclopentyl, or cyclohexyl.

31. The compound according to claim 26, wherein R6 is hydrogen.

32. The compound according to claim 26, wherein the compound of Formula III is an enantiomer or diastereomer.

33. The compound according to claim 26, wherein R4, R5', R8', and R9' are hydrogen.

34. The compound according to claim 26, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

35. The compound according to claim 26, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

36. The compound according to claim 26, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

37. The compound according to claim 26 having Formula XII: ##STR251##

38-63. (canceled)

64. A pharmaceutical composition comprising the compound according to claim 26 and a pharmaceutically acceptable carrier.

65-66. (canceled)

67. A method of treating, preventing, or ameliorating one or more

symptoms associated with a respiratory syncytial virus (RSV) infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 26 and a pharmaceutically acceptable carrier.

68. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered orally, parenterally, transdermally, or mucosally.

69. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered in an amount from about 10 mg/kg/day to about 15 mg/kg/day.

70. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the mammal is a human subject.

71. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the human subject is a human infant.

72. A method of inhibiting membrane fusion associated events characteristic of a viral infection in a mammal comprising administering the compound of claim 26 and a pharmaceutically acceptable carrier.

73. A method of treating, preventing, or ameliorating one or more symptoms associated with a HPIV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 26 and a pharmaceutically acceptable carrier.

74. The compound of claim 26 which is a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, diastereomer, racemate or mixture of stereisomers.

L9 ANSWER 2 OF 4 USPATFULL on STN
2003:173906 Benzimidazole compounds and antiviral uses thereof.
Lackey, John William, Hillsborough, NC, UNITED STATES
Kinder, Daniel S., Apex, NC, UNITED STATES
Tvermoes, Nicolai A., Durham, NC, UNITED STATES
US 2003119754 A1 20030626
APPLICATION: US 2002-141839 A1 20020509 (10)
PRIORITY: US 2001-290038P 20010511 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound of the Formula I: ##STR247## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime,

phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R1 and R2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group; R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; X is a bond, straight chain or branched substituted or unsubstituted alkyl, -(alkyl)N--, -(alkyl)O--, --C.dbd.N--, carbonyl, phosphorus, or sulfur; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is an integer from 0 to about 4; with the proviso that compounds of Formula I do not include a compound where R1, R2, R3, R4, R4', R8, R8' are hydrogen, X is a bond, and n=0 or 1; or a compound where R3, R4, R4', R8, and R8' are hydrogen, X is a bond, n=0, one of R1 or R2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

2. The compound according to claim 1, wherein: R1 and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl group having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is least one C1-C4 alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or C1-C4 alkylamine; R3 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl C1-C8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered

heterocycloalkyl or heteroaryl having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent, is at least one hydroxy, fluoride, chloride, bromine, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, carboxylic acid, ester, amine, or C1-C4 alkylamine; R4, R4', R8, and R8' each independently is hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, carboxylic acid, ester, C1-C4 amide, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide; X is a bond, straight chain or branched substituted or unsubstituted C1-C4 alkyl, --(C1-C4 alkyl)N--, --(C1-C4 alkyl)O--, carbonyl, or sulfur; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is from 0 to about 1.

3. The compound according to claim 1, wherein: X is a bond, methylene, or ethylene; Y is nitrogen, phosphorus, oxygen, or sulfur, wherein, if Y is oxygen or sulfur, R2 is not present; and n is 1.

4. The compound according to claim 1, wherein: R3 is a substituted or unsubstituted phenyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted acridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted benzodioxanyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted phenylphenolyl, wherein, if present, the substituent is at least one C1-C4 alkyl, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, fluoride, chloride, or bromide; X is a methylene; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is 1.

5. The compound according to claim 1, wherein at least one of R1, R2, or R3is a benzimidazole.

6. The compound according to claim 5, wherein X is a bond or methylene, R3 is a 2-benzimidazole, and at least one of R1 or R2 is a 2-benzimidazole or 2-methylenebenzimidazole.

7. The compound according to claim 1, wherein the compound of Formula I is an enantiomer or diastereomer.

8. The compound according to claim 1, wherein R4' and R8' are hydrogen, methyl, methyl ester, ethyl ester, C1-C2 amide, carboxylic acid, methoxy, or sulfonamide.

9. The compound according to claim 1, wherein R4' and R8' are both hydrogen.

10. The compound according to claim 1, wherein R4, R4', R8, and R8' are all hydrogen.

11. The compound according to claim 1, wherein at least one of R4, R4', R8, or R8' is not hydrogen.

12. The compound according to claim 1, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

13. The compound according to claim 1, wherein at least three of R4, R4', R8, and R8' are not hydrogen.

14. The compound according to claim 1 having Formula VII: ##STR248##

15. The compound according to claim 1, wherein the compound is selected from the group consisting of: 1-(1H-Benzimidazol-2-ylmethyl)-2-morpholin-4-ylmethyl-1H-benzimidazole-5-carboxylic acid methyl ester; 1-(1H-Benzimidazol-2-ylmethyl)-2-morpholin-4-ylmethyl-1H-benzimidazole-6-carboxylic acid methyl ester; {1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidin-3-yl}-methanol; {1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidin-2-yl}-methanol; 2-{1-[1-(1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidin-2-yl}-ethanol; [1,2,4]Oxadiazol-3-ylmethyl-2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-1H-benzoimidazole; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-(3-trifluoromethyl-phenyl)piperazine; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-(4-trifluoromethyl-phenyl)piperazine; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-pyridin-2-ylpiperazine; (R)-{1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidin-2-yl}-methanol; (S)-1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid methyl ester; (S)-1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid amide; 2-{4-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperazin-1-yl}-acetamide; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidine-3-carboxylic acid 1 (1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl ester; and 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1 H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid 1-(1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl ester.

16. A compound of the Formula II: ##STR249## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt,. sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R1 and R2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group; R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone,

nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R_4, R_4', R_8, and R_8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkyl, hydroxy, halide, methoxy, ethoxy, amine, cyano. alkanoyl, imide, amine, amide, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, halogen, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

17. The compound according to claim 16, wherein R_1 and R_2 are each independently: C_1-C_8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or alkylamine.

18. The compound according to claim 16, wherein R_3 is C_1-C_4 straight chain or branched alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine.

19. The compound according to claim 16, wherein R_4, R_4', R_8, and R_8' are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, C_1-C_4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide.

20. The compound according to claim 16, wherein at least one of R_1, R_2, or R_3 is a benzimidazole.

21. The compound according to claim 16, wherein R_3 is a 2-benzimidazole, and at least one of R_1 or R_2 is a 2-benzimidazole or 2-methylene benzimidazole.

22. The compound according to claim 16, wherein the compound of Formula II is an enantiomer or diastereomer.

23. The compound according to claim 16, wherein R_4, R_4', R_8, and R_8' are hydrogen.

24. The compound according to claim 16, wherein at least one of R4, R4', R8, or R8' is not hydrogen.

25. The compound according to claim 16 having Formulas VIII, IX, X, or XI: ##STR250##

26. A compound of the Formula III: ##STR251## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, amide, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl, wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester, cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

27. The compound according to claim 26, wherein: R1, and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12

alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

28. The compound according to claim 26, wherein: R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

29. The compound according to claim 26, wherein: R6 is a saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, C1-C4 alkoxy, substituted or unsubstituted C2-C6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C1-C4 alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

30. The compound according to claim 26, wherein: R1 and R2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl, hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl, 2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-thiophenyl)ethyl, N-benzyl-4-piperidinyl, 3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl, cyclopentyl, or cyclohexyl.

31. The compound according to claim 26, wherein R6 is hydrogen.

32. The compound according to claim 26, wherein the compound of Formula III is an enantiomer or diastereomer.

33. The compound according to claim 26, wherein R4', R5', R8', and R9' are hydrogen.

34. The compound according to claim 26, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

35. The compound according to claim 26, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

36. The compound according to claim 26, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

37. The compound according claim 26 having Formula XII: ##STR252##

38. A compound of the Formula IV: ##STR253## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate,

enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: --R1--N--R2-- form a saturated or unsaturated substituted or unsubstituted heterocycloalkyl ring, substituted or unsubstituted heteroaryl ring, wherein, if present, the substituent is at least one substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkoxy, amides, sulfonamides, esters, hydroxy, halide, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, carbonyl, nitro, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R6, R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, or sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, alkanoyl, imide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl.

39. The compound according to claim 38, wherein: --R1--N--R2-- form a saturated or unsaturated, substituted or unsubstituted 3 to 7 membered cycloalkyl, substituted or unsubstituted 3 to 7 membered heterocycloalkyl, substituted or unsubstituted 3 to 7 membered heteroaryl, wherein, if present, the substituent is at least one

substituted or unsubstituted C1-C4 alkyl, substituted or unsubstituted C1-C4 alkoxy, C1-C4 esters, hydroxy, fluoride, chloride, bromide, substituted or unsubstituted 3 to 8 membered aryl, substituted or unsubstituted 4 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, carbonyl, or nitro.

40. The compound according to claim 38, wherein: R4, R4', R5, R5', R6, R8, R8', R9, and R9' are each independently hydrogen, C-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

41. The compound according to claim 38, wherein R4', R5', R8', and R9' are hydrogen.

42. The compound according to claim 38, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

43. The compound according to claim 38, wherein R5, R5', R9, and R9' are hydrogen.

44. The compound according to claim 38, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

45. The compound according to claim 38, wherein R6 is hydrogen.

46. The compound according to claim 38, wherein: --R1--N--R2-- form a 5, 6, or 8 membered ring; and R4, R4', R5, R5', R6, R8, R8', R9, and R9 are each independently are hydrogen C1-C2 alkyl, C1-C2 alkoxy, amine, C1-C2 alkylamine, fluoride, chloride, bromide, hydroxy, nitro, C1-C2 sulfide, or C1-C2 sulfonyl.

47. The compound according to claim 38, wherein the 5, 6, or 8 membered ring formed by --R1--N--R2-- is a pyrrolidinyl, piperidinyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, piperazinyl, quinolinyl, acridinyl, thiazole, morpholinyl, or unsubstituted or substituted phenyl wherein, if present, the substituent, if present, is at least one methyl, ethyl, ester, methanol, 2-ethanol, or aldehyde.

48. The compound according to claim 38, wherein: --R1--N--R2-- form a cyclic structure: 2,5-dihydropyrrolyl, 3,5-dimethylpyrrolidinyl, 2-hydroxymethylpyrrolidinyl, 2-(2-hydroxyethyl)piperidinyl, N-carbaldehydepiperazinyl, N-(3-trifluoromethylphenyl)piperazinyl, N-(4-hydroxyphenyl)piperazinyl, N-(benzylcarbate)piperazinyl, tetrahydrothiazolyl, N-(4-acetylphenyl)piperazinyl, or cyclooctazanyl.

49. The compound according to claim 38, wherein the compound of Formula IV is an enantiomer or diastereomer.

50. The compound according to claim 38 having Formula XII: ##STR254##

51. The compound according to claim 38 having Formula XIV: ##STR255##

52. A compound of the Formula V: ##STR256## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, alkanoyl, imide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl. R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R7, R7', R8, R8', R9, R9', R10, and R10' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro amide, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone,

nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and m is an integer from 0 to about 4.

53. The compound according to claim 52, wherein: R1 is saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12 alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

54. The compound according to claim 52, wherein: R3 is hydrogen, C1-C8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, carboxylic acid, ester, amine, or C1-C4 alkylamine.

55. The compound according to claim 52, wherein: R4, R4', R5, R5', R7, R7', R8, R8', R9, R9', R10, and R10' are each independently hydrogen, methyl, methyl ester, ethyl ester, C1-C2 amide, carboxylic acid, methoxy, or sulfonamide; R6 is hydrogen or benzimidazole; and m is 1.

56. The compound according to claim 52, wherein R4', R5', R7', R8', R9', and R10' are hydrogen.

57. The compound according to claim 52, wherein R1 is hydrogen.

58. The compound according to claim 52, wherein at least one R4, R4', R8, and R8', are not hydrogen.

59. The compound according to claim 52, wherein at least two R5, R5', R9, and R9', are not hydrogen.

60. The compound according to claim 52, wherein at least one R7, R7', R10, and R10' are not hydrogen.

61. A compound of the formula: ##STR257##

62. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition comprising the compound according to claim 16 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising the compound according to claim 26 and a pharmaceutically acceptable carrier.

65. A pharmaceutical composition comprising the compound according to claim 38 and a pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising the compound according to claim 52 and a pharmaceutically acceptable carrier.

67. A method of treating, preventing, or ameliorating one or more symptoms associated with a respiratory syncytial virus (RSV) infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

68. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered orally, parenterally, transdermally, or mucosally.

69. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered in an amount from about 10 mg/kg/day to about 15 mg/kg/day.

70. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the mammal is a human subject.

71. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the human subject is a human infant.

72. A method of inhibiting membrane fusion associated events characteristic of a viral infection in a mammal comprising administering the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

73. A method of treating, preventing, or ameliorating one or more symptoms associated with a HPIV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

L9 ANSWER 3 OF 4 USPATFULL on STN
2003:146272 Mass-based encoding and qualitative analysis of combinatorial libraries.
Geysen, Hendrik Mario, Charlottesville, VA, UNITED STATES
Kinder, Daniel Stuart, Research Triangle Park, NC, UNITED STATES
Wagner, Craig Daniel, Research Triangle Park, NC, UNITED STATES
GlaxoSmithKline, Research Triangle Park, NC, UNITED STATES, 27709-3398 (U.S. corporation)
US 2003100018 A1 20030529
APPLICATION: US 2002-172525 A1 20020806 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A mass-based, non-chemical method for recording the reaction of at least a portion of a reaction series on each of a plurality of unique solid supports, said method comprising: (a) preparing a plurality of agents each having a unique defined mass; (b) preparing a group of solid supports; (c) reacting each solid support group with a different chemical reagent under a controlled reaction condition; (d) mixing the product groups of step (c) together and then dividing said mixture of unique solid supports into a plurality of groups for a second intermediate or final stage; (e) repeating said reacting with a chemical reagent under a controlled reaction condition at least once to

provide a plurality of final products, having different products on the different individual unique solid supports; each of said unique defined mass agents being reacted with either: each of a group of unique solid supports; each of a group of first chemical reagents in a reaction series; each of a group of second chemical reagents in a reaction series; or each of a group of subsequently added chemical reagents in a reaction series; such that each of said group of unique solid supports, group of first chemical reagents, group of second chemical reagents or group of subsequent chemical reagents has been reacted with an agent having a defined mass that is different from any other defined mass agent reacted with any other of said groups; said unique defined mass agents being capable of being analyzed and wherein said analysis defines the choice of a first chemical reagent, reaction condition under which said first chemical reagent was added, second chemical reagent, reaction condition under which said second chemical reagent was added, subsequent chemical reagent, or reaction condition under which said subsequent chemical reagent was added.

2. A mass-based, non-chemical method for recording the reaction history of a reaction series on each of a plurality of unique solid supports, said method comprising: (a) reacting, at a mass block insertion stage, a plurality of agents each having a unique defined mass with each of a group of said unique solid supports, such that each of said group of unique solid supports has been reacted with an agent having a defined mass that is different from any other agent reacted with any other of said groups of said unique solid supports; (b) reacting each solid support group having a different defined mass agent with a different chemical reagent; (c) mixing said groups together and then dividing said plurality of unique solid supports into a plurality of groups for a second intermediate or final stage; (d) repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products on the different individual unique solid supports; said unique defined mass agents being capable of being analyzed and wherein said analysis defines the choice of a first chemical reagent.

3. The method as claimed in claim 1, wherein said defined mass agents are analyzed by mass spectroscopy.

4. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique single mass peak when analyzed by mass spectroscopy.

5. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique double mass peak when analyzed by mass spectroscopy.

6. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique pair of single mass peaks when analyzed by mass spectroscopy.

7. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique pair of double mass peaks when analyzed by mass spectroscopy.

8. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each generate a unique pattern of one or more mass peaks.

9. The method as claimed in claim 8, wherein said unique peak patterns for each of said defined mass agents can be expressed as a machine-readable pattern.

10. The method as claimed in claim 9, wherein said machine readable patterns are bar codes.

11. The method as claimed in claim 3, wherein said defined mass agents are selected so as to each independantly generate a unique mass spectrometry mass peak pattern selected from the group consisting of unique single mass peaks, unique double mass peaks, unique pairs of single mass peaks, unique pairs of double mass peaks, and unique peak patterns that are capable of being expressed as machine-readable patterns.

12. The method as claimed in claim 1, wherein said defined mass agent is analyzed by nuclear magnetic resonance spectroscopy.

13. The method as claimed in claim 12, wherein said defined mass agents are selected so as to each generate a unique pattern of one or more nuclear magnetic resonance peaks.

14. The method as claimed in claim 13, wherein said unique peak patterns for each of said defined mass agents can be expressed as a machine-readable pattern.

15. The method as claimed in claim 14, wherein said machine readable patterns are bar codes.

16. The method as claimed in claim 1, wherein said defined mass agent is analyzed by infrared spectroscopy or by Raman spectroscopy.

17. The method as claimed in claim 16, wherein said defined mass agents are selected so as to each generate a unique pattern of one or more infrared spectroscopy or Raman spectroscopy peaks.

18. The method as claimed in claim 17, wherein said unique peak patterns for each of said defined mass agents can be expressed as a machine-readable pattern.

19. The method as claimed in claim 18, wherein said machine readable patterns are bar codes.

20. The method as claimed in claim 1, wherein said first, second or subsequent reagent is a substrate for the determination of binding specificity to a chemical compound of interest.

21. The method as claimed in claim 3, wherein said mass spectroscopy analysis provides mass peaks capable of being recognized as representing encoded reagents.

22. The method as claimed in claim 1, wherein additional mass peaks are generated that serve as signature peaks for positive identification of relevant mass peaks.

23. The method as claimed in claim 1, wherein said plurality of defined mass agents are molecular entities that differ from one another by having at least one of their atoms substituted by a different isotope of that atom, provided that the chemical structural formula of said defined mass agents is the same.

24. The method as claimed in claim 23, wherein said plurality of defined mass agents are molecular entities that differ from one another by having at least one isotopic substitution at different atomic positions within the molecule provided that the chemical structural formula of

said defined mass agents is the same.

25. The method as claimed in claim 1, wherein said plurality of defined mass agents are regularly repeating molecular entities that differ from one another by an integral number of said repeating molecular entities.

26. The method as claimed in claim 1, wherein at least two groups of said unique solid supports are employed in each said reacting.

27. The method as claimed in claim 1, comprising the additional step of screening said final products on said unique solid supports for a characteristic of interest and identifying the reaction history of at least one final product having said characteristic of interest.

28. The method as claimed in claim 1, comprising the additional step of cleaving said final products from said solid supports and screening said final products.

29. The method as claimed in claim 1, wherein said analysis is automated.

30. The method as claimed in claim 10, wherein said reaction steps are automated.

31. A kit for encoding the reaction history of a plurality of reaction series, comprising a plurality of different isotopically distinguishable organic compounds, each of the compounds characterized by having distinguishable masses but having the same chemical composition and the same chemical properties, each compound encoding at least one bit of different physical information which can be determined by a physical measurement.

32. A kit as claimed in claim 31, wherein said compounds are mixed with one another in a plurality of discrete ratios to produce a plurality of isotope mixtures that are physically distinguishable from each other.

33. A kit as claimed in claim 32, wherein said compounds are mixed with one another in a series of regularly repeating increasing increments.

34. A kit as claimed in claim 31, wherein said compounds are of the formula: R--C where R is a suitable solid support which allows for attachment and detachment of a molecular moiety of choice; and C is an isotopically doped linker which allows for attachment and detachment from said solid supprt.

35. A kit as claimed in claim 31, wherein said compounds are of the formula: L_1-C-L_2 where L_1 is a covalent bond or an organic moiety; C is an isotopically doped linker; and L_2 is a covalent bond or an organic moiety.

36. A kit as claimed in claim 35, wherein L_1 and L_2 are the same.

37. A kit as claimed in claim 31, wherein said compounds are of the formula R-L_1-C-L_2 where R is a suitable solid support which allows for attachment and detachment of a molecular moiety of choice; L_1 is a covalent bond or an organic moiety; C is an isotopically doped linker; and L_2 is a covalent bond or an organic moiety.

38. A kit as claimed in claim 31, wherein said compounds are of the formula $(L)_{n1}$-$(C)_{n2}$ where n1 is an integer of from one to ten, n2 is an integer of from one to ten, L an organic moiety or a covalent

bond when n1 is one, and C is an isotopically doped linker.

39. A kit as claimed in claim 31, wherein said compounds are of the formula R-L-C where R is a suitable solid support which allows for attachment and detachment of a plurality of molecular moiety of choice; L is a covalent bond or an organic moiety; and C is an isotopically doped linker.

40. A kit as claimed in claim 31, wherein said compounds are of the formula L-C1A-B-D-C2 L is a covalent bond or an organic moiety; C1 is an isotopically doped linker; A is a first monomer in a reaction series, B is a second monomer in a reaction series, and D is a third monomer in a reaction series; and C2 is a second isotopically doped linker that can physically be the same as or different from C1.

41. A kit as claimed in claim 31, wherein said compounds are of the formula L-C1-A-B-C2 L is a covalent bond or an organic moiety; C1 is an isotopically doped linker; A is a first monomer in a reaction series, B is a second monomer in a reaction series; and C2 is a second isotopically doped linker that can physically be the same as or different from C1.

42. A kit as claimed in claim 31, wherein said compounds are of the formula L-C1-A-C2 L is a covalent bond or an organic moiety; C1 is an isotopically doped linker; A is a first monomer in a reaction series; and C2 is a second isotopically doped linker that can physically be the same as or different from C1.

43. A kit as claimed in claim 31, wherein said components are isotopically doped suitable solid supports.

44. A kit as claimed in claim 31, wherein said components are of the formula ##STR42## where R is a suitable solid support; L is a covalent bond or an organic moiety; C is an isotopically doped moiety; and A is a first chemical reagent in a reaction series.

45. A kit as claimed in claim 31, where said components are of the formula ##STR43## where R is a suitable solid support; L is a covalent bond or an organic moiety; C is an isotopically doped moiety; and A is a first chemical reagent in a reaction series.

46. A solid support characterized by having a unique defined mass agent and a ligand bound to the surface of said solid support.

47. A solid support characterized by having up to 20 discrete unique defined mass agents bound to the surface of said solid support.

48. A solid support as claimed in claim 46, wherein said ligand is an organic moiety.

49. A solid support as claimed in claim 46, wherein said ligand is bound to said unique defined mass agent.

50. A solid support as claimed in claim 46, wherein said ligand is a non-oligomer which is aliphatic, alicyclic, aromatic, heterocyclic or a combination thereof.

51. A solid support as claimed in claim 46, wherein said ligand is an oligomer which is an oligopeptide, oligonucleotide, oligosaccharide, polylipid, polyester, polyamide, polyurethane, polyurea, polyether, polyphosphorus where phosphorus is a derivative taken from the group

consisting of phosphate, phosphonate, phosphoramide, phosphonamide, phosphite, or phosfinamide, or polysulfur where sulfur is a derivative taken from the group consisting of sulfone, sulfonate, sulfite, sulfinamiide, or sulfenamide.

52. A solid support as claimed in claim 46, wherein said support is a resin bead of about 1 to 10000 μm in diameter.

53. A solid support as claimed in claim 46, wherein said support is a polystyrene resin bead of about 1 to 10000 μm in diameter.

54. A solid support characterized by being isotopically doped.

55. A solid support as claimed in claim 54, wherein said support is an isotopically doped resin bead.

56. A solid support as claimed in claim 55, wherein said support is an isotopically doped polystyrene resin bead of about 10 to 2000 μm in diameter.

57. A library comprising a plurality of solid supports as claimed in claim 46.

58. A library comprising a plurality of solid supports as claimed in claim 46, wherein said final products have been cleaved from said solid supports.

59. A process for identifying compounds having a characteristic of interest, which comprises screening a library as claimed in claim 57.

60. A process as claimed in claim 59, wherein the compounds have been cleaved from the solid support.

61. A process as claimed in claim 60, wherein said cleavage is between said solid support and said unique defined mass agent.

62. A mass-based, non-chemical method for generating machine or human-recognizable patterns to record the reaction history of a reaction series on each of a plurality of unique solid supports, said method comprising: (a) generating a set of agents each having a unique defined mass such that each agent differs from any other agent in the set by having a defined mass that is different from any other agent in the set; (b) generating a recognition pattern for each agent in said set; (c) reacting, at a mass block insertion stage, a plurality of agents each having a unique defined mass with each of a group of said unique solid supports, such that each of said group of unique solid supports has been reacted with an agent having a defined mass that is different from any other agent reacted with any other of said groups of said unique solid supports; (d) reacting each solid support group having a different defined mass agent with a different first chemical reagent; (e) mixing said groups together and then dividing said plurality of unique solid supports into a plurality of groups for a second intermediate or final stage; (f) optionally repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products on the different individual unique solid supports; (g) analyzing said products for a characteristic of interest, (h) further analyzing products found to have a characteristic of interest in step (g) by an analytical method that generates a like type of patterns as that type generated for the recognition patterns in step (b); and (i) comparing the analytical patterns generated in step (h) to said recognition patterns.

63. A mass-based, non-chemical method for generating machine-recognizable patterns to record the reaction history of a reaction series on each of a plurality of unique solid supports, said method comprising: (a) generating a set of agents each having a unique defined mass such that each agent differs from any other agent in the set by having a defined mass that is different from any other agent in the set; (b) generating a machine-recognizable recognition pattern for each agent in said set; (c) reacting, at a mass block insertion stage, a plurality of agents each having a unique defined mass with each of a group of said unique solid supports, such that each of said group of unique solid supports has been reacted with an agent having a defined mass that is different from any other agent reacted with any other of said groups of said unique solid supports; (d) reacting each solid support group having a different defined mass agent with a different first chemical reagent; (e) mixing said groups together and then dividing said plurality of unique solid supports into a plurality of groups for a second intermediate or final stage; (f) optionally repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products on the different individual unique solid supports; (g) analyzing said products for a characteristic of interest through the use of an analysis device; (h) further analyzing products found to have a characteristic of interest in step (g) by an analytical method that generates a like type of patterns as that type generated for the recognition patterns in step (b); and (i) comparing the analytical patterns generated in step (h) to said recognition patterns such that said unique defined mass agents are capable of being analyzed and identified.

64. The method as claimed in claim 63, wherein said identification in step (i) leads to the -ready identification of said first chemical reagent.

65. The method as claimed in claim 63, wherein said method steps are executed by suitable automation apparatus means and under the control of a suitable computer means.

66. The method as claimed in claim 63, wherein said analysis device is selected from the group consisting of a flourescence activation cell scanner, a chromatography column or a chromatography plate.

67. The method as claimed in claim 63, wherein said analytical method is selected from the group consisting of mass spectrometry, nuclear magnetic resonance spectroscopy, infrared spectroscopy or Raman spectroscopy.

68. The method as claimed in claim 63 wherein said analysis device is close coupled to said automation apparatus used in the method so as to be automated and under the control of a computer.

69. The method as claimed in claim 63, wherein said analytical method is executed by a corresponding device that is close coupled to said automation apparatus used in the method so as to be automated and under the control of a computer.

70. A database readily retrievable from a suitable data storage means comprised of the set of machine-readable patterns generated by the method as claimed in claim 63.

71. A mass-based, non-chemical method for generating machine or human-recognizable patterns to record the reaction history of a reaction sequence of interest selected from a reaction series on each of a plurality of unique solid supports, said method comprising: (a)

generating a set of agents each having a unique defined mass such that each agent differs from any other agent in the set by having a defined mass that is different from any other agent in the set; (b) generating a recognition pattern for each agent in said set; (c) reacting, at a mass block insertion stage, a plurality of agents each having a unique defined mass with each of a group of said unique solid supports, such that each of said group of unique solid supports has been reacted with an agent having a defined mass that is different from any other agent reacted with any other of said groups of said unique solid supports; (d) reacting each solid support group having a different defined mass agent with a different first chemical reagent; (e) mixing said groups together and then dividing said plurality of unique solid supports into a plurality of groups for a second intermediate or final stage; (f) optionally repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products on the different individual unique solid supports; (g) analyzing said products for a characteristic of interest; (h) further analyzing products found to have a characteristic of interest in step (g) by an analytical method that generates a like type of patterns as that type generated for the recognition patterns in step (b); (i) comparing the analytical patterns generated in step (h) to said recognition patterns; (j) evaluating said analytical patterns to arrive at a qualitative and quantitative assessment of the output of a reaction sequence of interest, thereby identifying all products, quantities and yields of each of incomplete reactions, side reactions and previously unknown reactions in said sequence of interest.

72. A mass-based, non-chemical method for recording the reaction history of a reaction series in solution, said method comprising: (a) preparing, a plurality of agents each having a unique defined mass within each of a group of solution reaction wells, such that each of said group of reaction wells contains an agent having a defined mass that is different from any other agent within any other of said reaction wells; (b) reacting each different defined mass agent with a different first chemical reagent in each well; (c) mixing said groups together in to a resulting batch and then dividing said batch into a plurality of wells for a second intermediate or final stage; (d) repeating said reacting with a chemical reagent at least once to provide a plurality of final products, having different products within said wells; said unique defined mass agents being capable of being analyzed and wherein said analysis defines the choice of said first chemical reagent.

73. A programmed computer system for executing a mass-based method for recording the reaction history of at least a portion of a reaction series of interest on each of a plurality of solid supports or in each or a plurality of reaction vessels, wherein one or more chemical reagents or chemical conditions are discretely identifiable by one or more recognition patterns and wherein said reaction series chemical products are subjected to analytical means that generate analytical patterns for each of said products; comprising: first input means for introducing unique recognition patterns into the computer system, each pattern representing one of a plurality of agents each having a unique defined mass; memory means for storing said recognition pattern; second input means for introducing said resultant analytical patterns; and means for comparing said resulting analytical patterns to said recognition patterns in order to generate an output which is the identity of one or more of said chemical reagents or chemical conditions.

74. The programmed computer system as claimed in claim 73, additionally comprising means for controlling a robot means for performing one or more steps of said reaction series of interest.

75. The programmed computer system as claimed in claim 73, additionally comprising means for generating said unique recognition patterns.

76. The programmed computer system as claimed in claim 73, additionally comprising means for subjecting said reaction products to analytical means and generating analytical patterns.

77. A mass-based, non-chemical method for identifying different chemical compounds in a mixture of said chemical compounds, said method comprising: (a) preparing a plurality of chemical agents each having a unique defined mass; (b) preparing a group of chemical compounds to be identified; each of said unique defined mass agents being chemically linked or reacted with each of said chemical compounds to be identified to form a plurality of unique covalently bound one-to-one pairs of unique defined mass agents with compounds to be identified; said unique defined mass agents being capable of being analyzed on the basis of its mass, and wherein said analysis thus identifies the chemical compound reacted with said analyzed mass agent.

78. A mass-based, non-chemical method for identifying a chemical compound, said method comprising: (a) preparing a chemical agent having a unique defined mass; (b) preparing a chemical compound to be identified; said unique defined mass agent being chemically linked or reacted with said chemical compound to be identified to form a unique covalently bound one-to-one pairing of unique defined mass agent with compound to be identified; said unique defined mass agent being capable of being analyzed on the basis of its mass, and wherein said analysis thus identifies the chemical compound reacted with said analyzed mass agent.

L9 ANSWER 4 OF 4 USPATFULL on STN
2002:290787 Mass-based encoding and qualitative analysis of combinatorial libraries.
Geysen, Hendrik Mario, Chapell Hill, NC, United States
Kinder, Daniel Stuart, Cary, NC, United States
Wagner, Craig Daniel, Chapel Hill, NC, United States
SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
US 6475807 B1 20021105
WO 9737953 19971016
APPLICATION: US 1998-91954 19980626 (9)
WO 1997-US5701 19970408 19980626 PCT 371 date
PRIORITY: US 1996-14970P 19960408 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for labeling a plurality of solid supports, said method comprising; dividing a batch of solid supports that each have a first link having a first cleavage site into two or more groups of solid supports; preparing a mixture of chemical moieties that are distinguishable from each other by mass to produce a set of machine readable codes; chemically labeling each solid support group with one of the codes of the set under controlled reaction conditions such that each solid support group is labeled with a different code that is attached to the first link; linking a second link having a second cleavage site and a synthesis site to each code on the solid support to provide a set of constructs that each have a connecting group comprising in series the first cleavage site, the machine-readable code, the second cleavage site, and the synthesis site, wherein the formula of the connecting group is: L1-C-L2 where L1 is the first cleavage site, C

is the code and L2 is the second cleavage site; selecting at least some of the solid supports having the connecting group L1-C-L2 from the batch; and reading the machine readable code of the selected solid supports.

2. The method as claimed in claim 1, wherein said machine readable codes comprise defined mass agents that are capable of being analyzed by mass spectroscopy.

3. The method as claimed in claim 2, wherein said defined mass agents are selected to generate a unique single mass peak when analyzed by mass spectroscopy.

4. The method as claimed in claim 2, wherein said defined mass agents are selected to generate a unique double mass peak when analyzed by mass spectroscopy.

5. The method as claimed in claim 2, wherein said defined mass agents are selected to generate a unique pair of single mass peaks when analyzed by mass spectroscopy.

6. The method as claimed in claim 2, wherein said defined mass agents are selected to generate a unique pair of double mass peaks when analyzed by mass spectroscopy.

7. The method as claimed in claim 2, wherein said defined mass agents are selected to generate a unique pattern of one or more mass peaks.

8. The method as claimed in claim 7, wherein said unique pattern for of said defined mass agents is expressible as a machine-readable pattern.

9. The method as claimed in claim 8, wherein said machine readable pattern comprises a bar code.

10. The method as claimed in claim 3, wherein said defined mass agents are selected to independently generate a unique mass spectrometry mass peak pattern selected from the group consisting of unique single mass peaks, unique double mass peaks, unique pairs of single mass peaks, unique pairs of double mass peaks, and unique peak patterns that are capable of being expressed as machine-readable patterns.

11. The method as claimed in claim 2, wherein said mass spectroscopy analysis provides mass peaks capable of being recognized as representing encoded reagents.

12. The method as claimed in claim 11, wherein additional mass peaks are generated that serve as signature peaks for positive identification of relevant mass peaks.

13. The method as claimed in claim 1, wherein said machine readable codes comprise a plurality of defined mass agents that are chemical moieties that differ from one another by having at least one of their atoms substituted by a different isotope of that atom, provided that the chemical structural formula of said defined mass agents is the same.

14. Deviously Once Amended) The method as claimed in claim 13, wherein said plurality of defined mass agents are chemical moieties that differ from one another by having at least one isotopic substitution at different atomic positions within the molecule provided that the chemical structural formula of said defined mass agents is the same.

15. The method as claimed in claim 1, wherein said machine readable

codes comprise a plurality of defied mass agents that are regularly repeating molecular entities that differ from one another by an integral number of said repeating molecular entities.

16. The method as claimed in claim 1, wherein at least two groups of said solid supports are employed in each said reacting.

17. The method as claimed in clam 1, wherein said reading step is automated.

18. The method as claimed in claim 1, wherein labeling and linking steps are automated.

19. The method as claimed in claim 1, wherein the chemical moieties are isotopically doped.

20. The method as claimed in claim 1, wherein the code is sequentially assembled in two units, wherein at least one of the units is prepared by reacting the mixture of chemical moieties.

21. The method as claimed in claim 1, wherein the chemical moieties are mixed with one another in a plurality of discrete ratios.

22. A method for labeling a plurality of solid supports to determine chemical reagents synthesized to the solid supports, said method comprising: dividing a batch of solid supports that each have a first link having a first cleavage site into two more groups of solid supports; preparing a mixture of chemical moieties that are distinguishable from each other by mass to produce a set of machine readable codes; chemically labeling each solid support group with one of the codes of the set under controlled reaction conditions such that each solid support group is labeled with a different code that is attached to the first link; linking a second link having a second cleavage site and a synthesis site to each code on the solid support to provide a set of constructs that each have a connecting group comprising in jenies the first cleavage site, the machine-readable code, the second cleavage site, and the synthesis site, wherein the formula of the connecting group is; L1-C-L2 where L1 is the first cleavage site, C is the code and L2 is the second cleavage site, wherein the chemical moieties are isotropically doped and are mixed with one another in a plurality of discrete ratios; subjecting the solid supports having the connecting group L1-C-L2 of each solid support group of the batch to a first chemical reagent; optionally combining two or more of the groups of the solid supports having the connecting group L1-C-L2 into a combined group of solid supports and then subjecting the combined group of solid supports to a second chemical reagent; selecting at least some of the solid supports from the combined group of solid supports; and reading the machine readable code of the selected solid supports to determine the first chemical reagent to which the solid supports were subjected.

```
=> e lackey john w/in
E1          1     LACKEY JESSE R/IN
E2          1     LACKEY JOHN P/IN
E3          5 --> LACKEY JOHN W/IN
E4          5     LACKEY JOHN WILLIAM/IN
E5          1     LACKEY JOSEPH A/IN
E6          1     LACKEY JOSHUA/IN
E7          1     LACKEY JR GARY R/IN
E8          1     LACKEY JR JOE/IN
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E9            1     LACKEY JR ROBERT W/IN
E10           5     LACKEY JR STANLEY A/IN
E11           6     LACKEY JR WALTER J/IN
E12           1     LACKEY KAREN/IN

=> s e3 or e4
              5 "LACKEY JOHN W"/IN
              5 "LACKEY JOHN WILLIAM"/IN
L10          10 "LACKEY JOHN W"/IN OR "LACKEY JOHN WILLIAM"/IN

=> s l10 and (conjugat? or heptad or HR1 or HR2)
         163821 CONJUGAT?
            842 HEPTAD
            521 HR1
            432 HR2
L11           5 L10 AND (CONJUGAT? OR HEPTAD OR HR1 OR HR2)

=> d l11,cbib,clm,1-5

L11  ANSWER 1 OF 5  USPATFULL on STN
2006:167854 Benzimidazole compounds and antiviral uses thereof.
    Lackey, John William, Hillsborough, NC, UNITED STATES
    Kinder, Daniel S., Apex, NC, UNITED STATES
    Tvermoes, Nicolai A., Durham, NC, UNITED STATES
    Trimeris, Inc. (U.S. corporation)
    US 2006142365 A1 20060629
    APPLICATION: US 2006-346758  A1  20060202 (11)
    PRIORITY: US 2001-290038P  20010511 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A compound of the Formula I:    ##STR249## or a pharmaceutically-
       acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer,
       diastereomer, racemate or mixture of stereoisomer thereof, wherein:
       R1 and R2 are each independently: hydrogen, saturated or
       unsaturated straight or branched substituted or unsubstituted alkyl,
       substituted or unsubstituted cycloalkyl, substituted or unsubstituted
       heterocycloalkyl, substituted or unsubstituted heterocycloaryl;
       substituted or unsubstituted aryl, substituted or unsubstituted
       heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if
       present, the substituent is at least one alkanoyl, imide, alkyl,
       hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide,
       alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester,
       azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester,
       cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon,
       polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone,
       lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime,
       phosphate, phosphinate, phosphonate, phosphonic acid, quaternary
       ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester,
       sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;
       R3 is hydrogen, halide, saturated or unsaturated straight or
       branched substituted or unsubstituted alkyl, hydroxy, substituted or
       unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or
       unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl,
       or substituted or unsubstituted heteroaryl; wherein, if present the
       substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide,
       methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal,
       acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide,
       carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin,
       diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon,
       halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone,
       nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate,
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phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4' , R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; X is a bond, straight chain or branched substituted or unsubstituted alkyl, -(alkyl)N--, -(alkyl)O--, --C.dbd.N--, carbonyl, phosphorus, or sulfur; Y is nitrogen; n=1 is an integer from 0 to about 1; with the proviso that compounds of Formula I do not include a compound where R1, R2, R3, R4, R4', R8, R8' are hydrogen, X is a bond, and n=0; or a compound where R3, R4, R4', R8, and R8' are hydrogen, X is a bond, n=0, one of R1 or R2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

2-25. (canceled)

26. The compound according to claim 1 having Formula III: ##STR250## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, amide, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic

acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester, cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

27. The compound according to claim 26, wherein: R1, and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12 alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

28. The compound according to claim 26, wherein: R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

29. The compound according to claim 26, wherein: R6 is a saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, C1-C4 alkoxy, substituted or unsubstituted C2-C6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C1-C4 alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

30. The compound according to claim 26, wherein: R1 and R2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl, hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl, 2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-thiophenyl)ethyl, N-benzyl-4-piperidinyl,

3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl, cyclopentyl, or cyclohexyl.

31. The compound according to claim 26, wherein R6 is hydrogen.

32. The compound according to claim 26, wherein the compound of Formula III is an enantiomer or diastereomer.

33. The compound according to claim 26, wherein R4, R5', R8', and R9' are hydrogen.

34. The compound according to claim 26, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

35. The compound according to claim 26, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

36. The compound according to claim 26, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

37. The compound according to claim 26 having Formula XII: ##STR251##

38-63. (canceled)

64. A pharmaceutical composition comprising the compound according to claim 26 and a pharmaceutically acceptable carrier.

65-66. (canceled)

67. A method of treating, preventing, or ameliorating one or more symptoms associated with a respiratory syncytial virus (RSV) infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 26 and a pharmaceutically acceptable carrier.

68. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered orally, parenterally, transdermally, or mucosally.

69. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered in an amount from about 10 mg/kg/day to about 15 mg/kg/day.

70. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the mammal is a human subject.

71. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the human subject is a human infant.

72. A method of inhibiting membrane fusion associated events characteristic of a viral infection in a mammal comprising administering the compound of claim 26 and a pharmaceutically acceptable carrier.

73. A method of treating, preventing, or ameliorating one or more symptoms associated with a HPIV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 26 and a pharmaceutically acceptable carrier.

74. The compound of claim 26 which is a pharmaceutically acceptable salt, solvate, hydrate, enantiomer, diastereomer, racemate or mixture of

stereisomers.

L11 ANSWER 2 OF 5 USPATFULL on STN
2004:215031 Hetero-substituted benzimidazole compounds and antiviral uses thereof.
Lackey, John William, Hillsborough, NC, UNITED STATES
US 2004166137 A1 20040826
APPLICATION: US 2003-704224 A1 20031106 (10)
PRIORITY: US 2002-424940P 20021108 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound of the Formula I: ##STR49## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: Z1, Z2, Z3 and Z4 are each independently nitrogen or carbon and at least one of Z1, Z2, Z3 and Z4 is carbon; R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R1 and R2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group; R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy,

polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; X is a bond, straight chain or branched substituted or unsubstituted alkyl, -(alkyl)N--, -(alkyl)O--, --C.dbd.N--, carbonyl, phosphorus, or sulfur; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is an integer from 0 to about 4; with the proviso that compounds of Formula I do not include a compound where R1, R2, R3, R4, R4', R8, R8' are hydrogen, X is a bond, and n=0 or 1; or a compound where R3, R4, R4', R8, and R8' are hydrogen, X is a bond, n=0, one of R1 or R2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

2. The compound according to claim 1, wherein: R1 and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted4 to 12 membered heterocycloalkyl or heteroaryl group having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is least one C1-C4 alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or C1-C4 alkylamine; R3 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl C1-C8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent, is at least one hydroxy, fluoride, chloride, bromine, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, carboxylic acid, ester, amine, or C1-C4 alkylamine; R4, R4', R8, and R8' each independently is hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, carboxylic acid, ester, C1-C4 amide, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide; X is a bond, straight chain or branched substituted or unsubstituted C1-C4 alkyl, --(C1-C4 alkyl)N--, --(C1-C4 alkyl)O--, carbonyl, or sulfur; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is from 0 to about 1.

3. The compound according to claim 1, wherein: X is a bond, methylene, or ethylene; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is 1.

4. The compound according to claim 1, wherein: R3 is a substituted or unsubstituted phenyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted acridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted benzodioxanyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted phenylphenolyl, wherein, if present, the substituent is at least one C1-C4 alkyl, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, fluoride, chloride, or bromide; X is a methylene; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is 1.

5. The compound according to claim 1, wherein at least one of R1, R2, or R3 is a benzimidazole.

6. The compound according to claim 5, wherein X is a bond or methylene, R3 is a 2-benzimidazole, and at least one of R1 or R2 is a 2-benzimidazole or 2-methylenebenzimidazole.

7. The compound according to claim 1, wherein the compound of Formula I is an enantiomer or diastereomer.

8. The compound according to claim 1, wherein R4' and R8' are hydrogen, methyl, methyl ester, ethyl ester, C1-C2 amide, carboxylic acid, methoxy, or sulfonamide.

9. The compound according to claim 1, wherein R4' and R8' are both hydrogen.

10. The compound according to claim 1, wherein R4, R4', R8, and R8' are all hydrogen.

11. The compound according to claim 1, wherein at least one of R4, R4', R8, or R8' is not hydrogen.

12. The compound according to claim 1, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

13. The compound according to claim 1, wherein at least three of R4, R4', R8, and R8' are not hydrogen.

14. The compound according to claim 1, wherein at least one of Z2 and Z4 is nitrogen.

15. The compound according to claim 1, wherein both of Z2 and Z4 are nitrogen.

16. The compound according to claim 1, wherein Z4 is nitrogen.

17. A compound of the Formula II: ##STR50## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: Z1, Z2, Z3 and Z4 are each independently nitrogen or carbon and at least one of Z1, Z2, Z3 and Z4 is carbon; R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R1 and R2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group; R3 is

hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R_4, R_4', R_8, and R_8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkyl, hydroxy, halide, methoxy, ethoxy, amine, cyano, alkanoyl, imide, amine, amide, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, halogen, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl.

18. The compound according to claim 17, wherein R_1 and R_2 are each independently: C_1-C_8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl,4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or alkylamine.

19. The compound according to claim 16, wherein R_3 is C_1-C_4 straight chain or branched alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine.

20. The compound according to claim 17, wherein R_4, R_4', R_8, and R_8' are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, C_1-C_4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide.

21. The compound according to claim 17, wherein at least one of R_1, R_2, or R_3 is a benzimidazole.

22. The compound according to claim 17, wherein R_3 is a 2-benzimidazole, and at least one of R_1 or R_2 is a 2-benzimidazole or 2-methylene benzimidazole.

23. The compound according to claim 17, wherein the compound of Formula II is an enantiomer or diastereomer.

24. The compound according to claim 17, wherein R_4, R_4', R_8, and R_8' are hydrogen.

25. The compound according to claim 17, wherein at least one of R_4, R_4', R_8, or R_8' is not hydrogen.

26. The compound according to claim 17, wherein at least one of Z_2 and Z_4 is nitrogen.

27. The compound according to claim 17, wherein both of Z_2 and Z_4 are nitrogen.

28. The compound according to claim 17, wherein Z_4 is nitrogen.

29. A compound of the Formula III: ##STR51## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon; Z_5, Z_6, Z_7 and Z_8 are each independently nitrogen or carbon; R_1 and R_2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, amide, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R_4, R_4', R_5, R_5', R_8, R_8', R_9, and R_9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide,

sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester, cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

30. The compound according to claim 29, wherein: R1, and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12 alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

31. The compound according to claim 29, wherein: R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

32. The compound according to claim 29, wherein: R6 is a saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, C1 -C4 alkoxy, substituted or unsubstituted C2-C6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C1-C4 alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

33. The compound according to claim 29, wherein: R1 and R2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl, hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl, 2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-thiophenyl)ethyl, N-benzyl-4-piperidinyl, 3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl, cyclopentyl, or cyclohexyl.

34. The compound according to claim 29, wherein R6 is hydrogen.

35. The compound according to claim 29, wherein the compound of Formula III is an enantiomer or diastereomer.

36. The compound according to claim 29, wherein R4', R5', R8', and R9' are hydrogen.

37. The compound according to claim 29, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

38. The compound according to claim 29, wherein at least two of R4, R4', R8', and R8' are not hydrogen.

39. The compound according to claim 29, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

40. The compound according to claim 29, wherein at least one of Z2 and Z4 is nitrogen.

41. The compound according to claim 29, wherein both of Z2 and Z4 are nitrogen.

42. The compound according to claim 29, wherein Z4 is nitrogen.

43. The compound according to claim 29 having Formula V: ##STR52##

44. A compound of the Formula IV: ##STR53## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: Z1, Z2, Z3 and Z4 are each independently nitrogen or carbon and at least one of Z1, Z2, Z3 and Z4 is carbon; Z5, Z6, Z7 and Z8 are each independently nitrogen or carbon; --R1--N--R2-- form a saturated or unsaturated substituted or unsubstituted heterocycloalkyl ring, substituted or unsubstituted heteroaryl ring, wherein, if present, the substituent is at least one substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkoxy, amides, sulfonamides, esters, hydroxy, halide, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, carbonyl, nitro, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, or sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid

ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, alkanoyl, imide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl.

45. The compound according to claim 44, wherein: --R1--N--R2-- form a saturated or unsaturated, substituted or unsubstituted 3 to 7 membered cycloalkyl, substituted or unsubstituted 3 to 7 membered heterocycloalkyl, substituted or unsubstituted 3 to 7 membered heteroaryl, wherein, if present, the substituent is at least one substituted or unsubstituted C1-C4 alkyl, substituted or unsubstituted C1-C4 alkoxy, C1-C4 esters, hydroxy, fluoride, chloride, bromide, substituted or unsubstituted 3 to 8 membered aryl, substituted or unsubstituted 4 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, carbonyl, or nitro.

46. The compound according to claim 44, wherein: R4, R4', R5, R5', R6, R8, R8', R9, and R9' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

47. The compound according to claim 44, wherein R4', R5', R8', and R9' are hydrogen.

48. The compound according to claim 44 wherein at least one of R4, R4', R8, and R8' is not hydrogen.

49. The compound according to claim 44, wherein R5, R5', R9, and R9' are hydrogen.

50. The compound according to claim 44, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

51. The compound according to claim 44, wherein R6 is hydrogen.

52. The compound according to claim 44, wherein: --R1--N--R2-- form a 5, 6, or 8 membered ring; and R4, R4', R5, R5', R6, R8, R8', R9, and R9 are each independently are hydrogen C1-C2 alkyl, C1-C2

alkoxy, amine, C1-C2 alkylamine, fluoride, chloride, bromide, hydroxy, nitro, C1-C2 sulfide, or C1-C2 sulfonyl.

53. The compound according to claim 44, wherein the 5, 6, or 8 membered ring formed by --R1--N--R2-- is a pyrrolidinyl, piperidinyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, piperazinyl, quinolinyl, acridinyl, thiazole, morpholinyl, or unsubstituted or substituted phenyl wherein, if present, the substituent, if present, is at least one methyl, ethyl, ester, methanol, 2-ethanol, or aldehyde.

54. The compound according to claim 44, wherein the compound of Formula IV is an enantiomer or diastereomer.

55. The compound according to claim 44, wherein at least one of Z2 and Z4 is nitrogen.

56. The compound according to claim 44, wherein both of Z2 and Z4 are nitrogen.

57. The compound according to claim 44, wherein Z4 is nitrogen.

58. The compound according to claim 44 having Formula VI: ##STR54##

59. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

60. A pharmaceutical composition comprising the compound according to claim 17 and a pharmaceutically acceptable carrier.

61. A pharmaceutical composition comprising the compound according to claim 29 and a pharmaceutically acceptable carrier.

62. A pharmaceutical composition comprising the compound according to claim 43 and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition comprising the compound according to claim 44 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising the compound according to claim 58 and a pharmaceutically acceptable carrier.

65. A method of treating, preventing, or ameliorating one or more symptoms associated with a respiratory syncytial virus (RSV) infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

66. The method of treating, preventing, or ameliorating a viral infection according to claim 65, wherein the compound is administered orally, parenterally, transdermally, or mucosally.

67. The method of treating, preventing, or ameliorating a viral infection according to claim 65, wherein the compound is administered in an amount from about 10 mg/kg/day to about 15 mg/kg/day.

68. The method of treating, preventing, or ameliorating a viral infection according to claim 65, wherein the mammal is a human subject.

69. The method of treating, preventing, or ameliorating a viral infection according to claim 68, wherein the human subject is a human infant.

70. A method of inhibiting membrane fusion associated events characteristic of a viral infection in a mammal comprising administering the compound of claim 1 and a pharmaceutically acceptable carrier.

71. A method of treating, preventing, or ameliorating one or more symptoms associated with a HPV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

72. A method of treating, preventing, or ameliorating one or more symptoms associated with a hMPV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

L11 ANSWER 3 OF 5 USPATFULL on STN
2004:159410 **Conjugates** comprised of polymer and HIV gp41-derived peptides and their use in therapy.
Bray, Brian, Graham, NC, UNITED STATES
Kang, Myung-Chol, Chapel Hill, NC, UNITED STATES
Tvermoes, Nicolai, Durham, NC, UNITED STATES
Kinder, Daniel, Durham, NC, UNITED STATES
Lackey, John William, Hillsborough, NC, UNITED STATES
US 2004122214 A1 20040624
APPLICATION: US 2003-671282 A1 20030924 (10)
PRIORITY: US 2002-414439P 20020927 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A **conjugate** comprising a polymer to which is operably bound no less than two molecules of synthetic peptides, wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a **heptad** repeat region of Human Immunodeficiency Virus (HIV) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the **conjugate** has durability comprising antiviral activity against HIV strains resistant to synthetic peptide alone.

2. The **conjugate** according to claim 1, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

3. The **conjugate** according to claim 2, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

4. The **conjugate** according to claim 1, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of HIV gp41.

5. The **conjugate** according to claim 4, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

6. The **conjugate** according to claim 1, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of HIV gp41.

7. The **conjugate** according to claim 6, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

8. The **conjugate** according to claim 1, wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of HIV gp41, and wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of HIV gp41.

9. The **conjugate** according to claim 1, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

10. A method of making a **conjugate**, the method comprising the steps of: (a) reacting a first molecule of synthetic peptide with a polymer in forming an intermediate comprising a first intermediate, wherein the first molecule of synthetic peptide operably binds to a first reactive functionality of the polymer; and (b) reacting the intermediate comprising the first intermediate with a second molecule of synthetic peptide, wherein the second molecule of synthetic peptide operably binds to the intermediate comprising the first intermediate via a second reactive functionality of the polymer, in forming a **conjugate** comprised of a polymer to which is operably bound no less than two molecules of synthetic peptides; and wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a **heptad** repeat region of Human Immunodeficiency Virus (HIV) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the **conjugate** has durability comprising antiviral activity against HIV strains resistant to synthetic peptide alone.

11. The method according to claim 10, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

12. The method according to claim 11, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

13. The method according to claim 10, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of HIV gp41.

14. The method according to claim 13, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

15. The method according to claim 10, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of HIV gp41.

16. The method according to claim 15, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

17. The method according to claim 10, wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of HIV gp41, and wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of HIV gp41.

18. The method according to claim 10, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

19. A method of inhibiting transmission of HIV to a target cell, the method comprising adding to the virus and the cell an amount of **conjugate** effective to inhibit infection of the cell by the virus; wherein the **conjugate** comprises a polymer to which is operably bound no less than two molecules of synthetic peptides, wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a **heptad** repeat region of Human Immunodeficiency Virus (HIV) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the **conjugate** has durability comprising antiviral activity against HIV strains resistant to synthetic peptide alone.

20. The method according to claim 19, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

21. The method according to claim 20, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

22. The method according to claim 19, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of HIV gp41.

23. The method according to claim 22, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

24. The method according to claim 19, wherein each synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of HIV gp41.

25. The method according to claim 24, wherein each synthetic peptide of the **conjugate** comprises an identical amino acid sequence.

26. The method according to claim 19, wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR1** region of HIV gp41, and wherein at least one molecule of synthetic peptide of the **conjugate** comprises an amino acid sequence derived from the **HR2** region of HIV gp41.

27. The method according to claim 19, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

28. The method according to claim 19, wherein the **conjugate** inhibits fusion between the virus and the target cell in inhibiting infection of the cell by the virus.

29. The method according to claim 19, wherein the **conjugate** further comprises a pharmaceutically acceptable carrier.

30. The method according to claim 29, wherein the **conjugate** is administered to an HIV-infected individual.

L11 ANSWER 4 OF 5 USPATFULL on STN
2004:146900 Methods and compositions for inhibition of membrane fusion-associated events, including HIV transmission.
Jeffs, Peter, Chapel Hill, NC, United States

Lackey, John William, Hillsborough, NC, United States
Erickson, Joel Burton, Durham, NC, United States
Lawless, Mary Katherine, Raleigh, NC, United States
Merutka, Gene, Saratoga, CA, United States
Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6750008 B1 20040615
APPLICATION: US 1999-350841 19990709 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for identifying a compound that inhibits formation of or disrupts a DP107-like peptide/DP178-like peptide complex, said method comprising: (a) contacting, both in the presence and in the absence of a test compound, (i) a DP107-like peptide, wherein the DP107-like peptide is selected from the group consisting of DP107 (SEQ ID NO:16) and M41Δ178 (SEQ ID NO:1649), and (ii) a DP178-like peptide consisting of 16 to 39 amino acid residues in length, further comprising 16 to 36 amino acid residues of the DP178 amino acid sequence (SEQ ID NO:15), wherein the peptide has one, two or three amino acid residue substitutions to the DP178 sequence, further wherein the peptide has reduced binding affinity for the DP107-like peptide relative to that of DP178 (SEQ ID NO:15); and (b) determining the binding affinity of the DP178-like peptide and the DP107-like peptide in both the presence and in the absence of the test compound under conditions sufficient for binding of the peptides, wherein a lower binding affinity in the presence of the test compound indicates that the test compound inhibits formation of or disrupts a DP107-like/DP178-like complex, and wherein the DP107-like peptide and the DP-178-like peptide each comprise an amino acid sequence identified by one or more of the ALLMOTIS, 107x178x4 or PLZIP sequence search motifs.

2. The method of claim 1, wherein the binding affinities are determined by means of fluorescence polarization.

3. The method of claim 1, wherein the test compound is a peptide.

4. The method of claim 1, wherein the test compound is a small molecule.

5. A method for identifying a compound that inhibits formation of or disrupts a DP107-like peptide/DP178-like peptide complex, said method comprising: (a) contacting, both in the presence and the absence of a test compound, (i) a DP107-like peptide, wherein the DP107-like peptide is selected from the group consisting of DP107 (SEQ ID NO:16) and M41Δ178 (SEQ ID NO:1649), and (ii) a DP178-like peptide having reduced binding affinity for the DP107-like peptide relative to that of DP178 (SEQ ID NO:15), wherein the DP178-like peptide is selected from the group consisting of T1660 (SEQ ID NO:1515), T1661 (SEQ ID NO:1516), T1659 (SEQ ID NO:1514), T1631 (SEQ ID NO:1493), T1628 (SEQ ID NO:1490), T878 (SEQ ID NO:758), T870 (SEQ ID NO:750), T869 (SEQ ID NO:749), T868 (SEQ ID NO:748) and M41Δ107 (SEQ ID NO:1650); and (b) determining the binding affinity of the DP178-like peptide and the DP107-like peptide in both the presence and the absence of the test compound under conditions sufficient for binding of the peptides, wherein a lower binding affinity in the presence of the test compound indicates that the test compound inhibits formation of or disrupts a DP107-like/DP178-like complex.

6. The method of claim 5, wherein the binding affinities are determined by means of fluorescence polarization.

7. The method of claim 5, wherein the test compound is a peptide.

8. The method of claim 5, wherein the test compound is a small molecule.

9. The method of claim 1, wherein the amino acid substitution is in a residue selected from the group consisting of residues at positions corresponding to L4, I5, I9, E20 and L26 within the DP178 (SEQ ID NO:15) amino acid sequence.

10. The method of claim 9, wherein there is one amino acid substitution.

11. The method of claim 1, wherein the DP178-like peptide consists of an amino acid sequence of 36 amino acids in length.

12. The method of claim 11, wherein the amino acid substitution is in a residue selected from the group consisting of residues at positions corresponding to L4, I5, I9, E20 and L26 within the DP178 (SEQ ID NO:15) amino acid sequence.

13. The method of claim 12, wherein there is one amino acid substitution.

14. A method for identifying a compound that inhibits formation of or disrupts a DP107-like peptide/DP178-like peptide complex, said method comprising: (a) contacting, both in the presence and in the absence of a test compound, (i) a DP107-like peptide, wherein the DP107-like peptide is selected from the group consisting of DP107 (SEQ ID NO:16) and M41Δ178 (SEQ ID NO:1649), and (ii) a DP178-like peptide having reduced binding affinity for the DP107-like peptide, wherein the DP178-like peptide possesses no less than one and no more than three amino acid substitutions in the amino acid sequence of peptide DP178 (SEQ ID NO:15); and (b) determining the binding affinity of the DP178-like peptide and the DP107-like peptide in both the presence and in the absence of the test compound under conditions sufficient for binding of the peptides, wherein a lower binding affinity in the presence of the test compound indicates that the test compound inhibits formation of or disrupts a DP107-like/DP178-like complex; and wherein the DP107-like peptide and the DP178-like peptide each consist of an amino acid sequence of between 16 and 39 amino acids identified by one or more of the ALLMOTI5, 107x178x4 or PLZIP sequence search motifs.

15. The method of claim 14, wherein the binding affinities are determined by means of fluorescence polarization.

16. The method of claim 14, wherein the test compound is a peptide.

17. The method of claim 14, wherein the test compound is a small molecule.

18. The method of claim 14, wherein the amino acid substitution is in a residue selected from the group consisting of residues at positions corresponding to L4, I5, I9, E20 and L26 within the DP178 (SEQ ID NO:15) amino acid sequence.

19. The method of claim 18, wherein there is one amino acid substitution.

20. The method of claim 14, wherein the DP178-like peptide consists of an amino acid sequence of 36 amino acids in length.

21. The method of claim 20, wherein the amino acid substitution is in a residue selected from the group consisting of residues at positions corresponding to L4, I5, I9, E20 and L26 within

the DP178 (SEQ ID NO:15) amino acid sequence.

22. The method of claim 21, wherein there is one amino acid substitution.

L11 ANSWER 5 OF 5 USPATFULL on STN
2003:173906 Benzimidazole compounds and antiviral uses thereof.
Lackey, John William, Hillsborough, NC, UNITED STATES
Kinder, Daniel S., Apex, NC, UNITED STATES
Tvermoes, Nicolai A., Durham, NC, UNITED STATES
US 2003119754 A1 20030626
APPLICATION: US 2002-141839 A1 20020509 (10)
PRIORITY: US 2001-290038P 20010511 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound of the Formula I: ##STR247## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R1 and R2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group; R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid

ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; X is a bond, straight chain or branched substituted or unsubstituted alkyl, -(alkyl)N--, -(alkyl)O--, --C.dbd.N--, carbonyl, phosphorus, or sulfur; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is an integer from 0 to about 4; with the proviso that compounds of Formula I do not include a compound where R1, R2, R3, R4, R4', R8, R8' are hydrogen, X is a bond, and n=0 or 1; or a compound where R3, R4, R4', R8, and R8' are hydrogen, X is a bond, n=0, one of R1 or R2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

2. The compound according to claim 1, wherein: R1 and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl group having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is least one C1-C4 alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or C1-C4 alkylamine; R3 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl C1-C8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent, is at least one hydroxy, fluoride, chloride, bromine, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, carboxylic acid, ester, amine, or C1-C4 alkylamine; R4, R4', R8, and R8' each independently is hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, carboxylic acid, ester, C1-C4 amide, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide; X is a bond, straight chain or branched substituted or unsubstituted C1-C4 alkyl, --(C1-C4 alkyl)N--, --(C1-C4 alkyl)O--, carbonyl, or sulfur; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is from 0 to about 1.

3. The compound according to claim 1, wherein: X is a bond, methylene, or ethylene; Y is nitrogen, phosphorus, oxygen, or sulfur, wherein, if Y is oxygen or sulfur, R2 is not present; and n is 1.

4. The compound according to claim 1, wherein: R3 is a substituted or unsubstituted phenyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted acridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted benzodioxanyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted phenylphenolyl, wherein, if present, the substituent is at least one C1-C4 alkyl, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, fluoride,

chloride, or bromide; X is a methylene; Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R2 is not present; and n is 1.

5. The compound according to claim 1, wherein at least one of R1, R2, or R3is a benzimidazole.

6. The compound according to claim 5, wherein X is a bond or methylene, R3 is a 2-benzimidazole, and at least one of R1 or R2 is a 2-benzimidazole or 2-methylenebenzimidazole.

7. The compound according to claim 1, wherein the compound of Formula I is an enantiomer or diastereomer.

8. The compound according to claim 1, wherein R4' and R8' are hydrogen, methyl, methyl ester, ethyl ester, C1-C2 amide, carboxylic acid, methoxy, or sulfonamide.

9. The compound according to claim 1, wherein R4' and R8' are both hydrogen.

10. The compound according to claim 1, wherein R4, R4', R8, and R8' are all hydrogen.

11. The compound according to claim 1, wherein at least one of R4, R4', R8, or R8' is not hydrogen.

12. The compound according to claim 1, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

13. The compound according to claim 1, wherein at least three of R4, R4', R8, and R8' are not hydrogen.

14. The compound according to claim 1 having Formula VII: ##STR248##

15. The compound according to claim 1, wherein the compound is selected from the group consisting of: 1-(1H-Benzimidazol-2-ylmethyl)-2-morpholin-4-ylmethyl-1H-benzimidazole-5-carboxylic acid methyl ester; 1-(1H-Benzimidazol-2-ylmethyl)-2-morpholin-4-ylmethyl-1H-benzimidazole-6-carboxylic acid methyl ester; {1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidin-3-yl}-methanol; {1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidin-2-yl}-methanol; 2-{1-[1-(1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidin-2-yl}-ethanol; [1,2,4]Oxadiazol-3-ylmethyl-2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-1H-benzoimidazole; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-(3-trifluoromethyl-phenyl)piperazine; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-(4-trifluoromethyl-phenyl)piperazine; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-4-pyridin-2-ylpiperazine; (R)-{1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidin-2-yl}-methanol; (S)-1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid methyl ester; (S)-1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid amide; 2-{4-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperazin-1-yl}-acetamide; 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl]-piperidine-3-carboxylic acid 1 (1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl ester; and 1-[1-(1H-Benzoimidazol-2-ylmethyl)-1 H-benzoimidazol-2-ylmethyl]-pyrrolidine-2-carboxylic acid 1-(1H-benzoimidazol-2-ylmethyl)-1H-benzoimidazol-2-ylmethyl ester.

16. A compound of the Formula II: ##STR249## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt,. sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R1 and R2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group; R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R8, and R8' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkyl, hydroxy, halide, methoxy, ethoxy, amine, cyano. alkanoyl, imide, amine, amide, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, halogen, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

17. The compound according to claim 16, wherein R1 and R2 are each independently: C1-C8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if

present, the substituent is at least one hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or alkylamine.

18. The compound according to claim 16, wherein R3 is C1-C4 straight chain or branched alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, carboxylic acid, ester, amine, or C1-C4 alkylamine.

19. The compound according to claim 16, wherein R4, R4', R8, and R8' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

20. The compound according to claim 16, wherein at least one of R1, R2, or R3 is a benzimidazole.

21. The compound according to claim 16, wherein R3 is a 2-benzimidazole, and at least one of R1 or R2 is a 2-benzimidazole or 2-methylene benzimidazole.

22. The compound according to claim 16, wherein the compound of Formula II is an enantiomer or diastereomer.

23. The compound according to claim 16, wherein R4, R4', R8, and R8' are hydrogen.

24. The compound according to claim 16, wherein at least one of R4, R4', R8, or R8' is not hydrogen.

25. The compound according to claim 16 having Formulas VIII, IX, X, or XI: ##STR250##

26. A compound of the Formula III: ##STR251## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 and R2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, amide, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy,

substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl, wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated,saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester, cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

27. The compound according to claim 26, wherein: R1, and R2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12 alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

28. The compound according to claim 26, wherein: R4, R4', R5, R5', R8, R8', R9, and R9' are each independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

29. The compound according to claim 26, wherein: R6 is a saturated or unsaturated straight or branched substituted or unsubstituted C1-C8 alkyl, C1-C4 alkoxy, substituted or unsubstituted C2-C6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C1-C4 alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

30. The compound according to claim 26, wherein: R1 and R2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl, hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl, 2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-thiophenyl)ethyl, N-benzyl-4-piperidinyl, 3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl, cyclopentyl, or cyclohexyl.

31. The compound according to claim 26, wherein R6 is hydrogen.

32. The compound according to claim 26, wherein the compound of Formula III is an enantiomer or diastereomer.

33. The compound according to claim 26, wherein R4', R5', R8', and R9' are hydrogen.

34. The compound according to claim 26, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

35. The compound according to claim 26, wherein at least two of R4, R4', R8, and R8' are not hydrogen.

36. The compound according to claim 26, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

37. The compound according claim 26 having Formula XII: ##STR252##

38. A compound of the Formula IV: ##STR253## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: --R1--N--R2-- form a saturated or unsaturated substituted or unsubstituted heterocycloalkyl ring, substituted or unsubstituted heteroaryl ring, wherein, if present, the substituent is at least one substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkoxy, amides, sulfonamides, esters, hydroxy, halide, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, carbonyl, nitro, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R6, R8, R8', R9, and R9' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic

acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, or sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate; phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, alkanoyl, imide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl.

39. The compound according to claim 38, wherein: --R1--N--R2-- form a saturated or unsaturated, substituted or unsubstituted 3 to 7 membered cycloalkyl, substituted or unsubstituted 3 to 7 membered heterocycloalkyl, substituted or unsubstituted 3 to 7 membered heteroaryl, wherein, if present, the substituent is at least one substituted or unsubstituted C1-C4 alkyl, substituted or unsubstituted C1-C4 alkoxy, C1-C4 esters, hydroxy, fluoride, chloride, bromide, substituted or unsubstituted 3 to 8 membered aryl, substituted or unsubstituted 4 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, carbonyl, or nitro.

40. The compound according to claim 38, wherein: R4, R4', R5, R5', R6, R8, R8', R9, and R9' are each independently hydrogen, C-C4 alkyl, C1-C4 alkoxy, amine, C1-C4 alkylamine, C1-C4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C1-C4 sulfide, C1-C4 sulfonyl, or sulfonamide.

41. The compound according to claim 38, wherein R4', R5', R8', and R9' are hydrogen.

42. The compound according to claim 38, wherein at least one of R4, R4', R8, and R8' is not hydrogen.

43. The compound according to claim 38, wherein R5, R5', R9, and R9' are hydrogen.

44. The compound according to claim 38, wherein at least one of R5, R5', R9, and R9' is not hydrogen.

45. The compound according to claim 38, wherein R6 is hydrogen.

46. The compound according to claim 38, wherein: --R1--N--R2--

form a 5, 6, or 8 membered ring; and R4, R4', R5, R5', R6, R8, R8', R9, and R9 are each independently are hydrogen C1-C2 alkyl, C1-C2 alkoxy, amine, C1-C2 alkylamine, fluoride, chloride, bromide, hydroxy, nitro, C1-C2 sulfide, or C1-C2 sulfonyl.

47. The compound according to claim 38, wherein the 5, 6, or 8 membered ring formed by --R1--N--R2-- is a pyrrolidinyl, piperidinyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, piperazinyl, quinolinyl, acridinyl, thiazole, morpholinyl, or unsubstituted or substituted phenyl wherein, if present, the substituent, if present, is at least one methyl, ethyl, ester, methanol, 2-ethanol, or aldehyde.

48. The compound according to claim 38, wherein: --R1--N--R2-- form a cyclic structure: 2,5-dihydropyrrolyl, 3,5-dimethylpyrrolidinyl, 2-hydroxymethylpyrrolidinyl, 2-(2-hydroxyethyl)piperidinyl, N-carbaldehydepiperazinyl, N-(3-trifluoromethylphenyl)piperazinyl, N-(4-hydroxyphenyl)piperazinyl, N-(benzylcarbate)piperazinyl, tetrahydrothiazolyl, N-(4-acetylphenyl)piperazinyl, or cyclooctazanyl.

49. The compound according to claim 38, wherein the compound of Formula IV is an enantiomer or diastereomer.

50. The compound according to claim 38 having Formula XII: ##STR254##

51. The compound according to claim 38 having Formula XIV: ##STR255##

52. A compound of the Formula V: ##STR256## or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein: R1 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, alkanoyl, imide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl. R3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal,

thiocarboxylic acid, thiol, or thioaryl; R4, R4', R5, R5', R7, R7', R8, R8', R9, R9', R10, and R10' are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; R6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro amide, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and m is an integer from 0 to about 4.

53. The compound according to claim 52, wherein: R1 is saturated or unsaturated straight or branched substituted or unsubstituted C1-C11 alkyl, C1-C12 alkoxy, substituted or unsubstituted C1-C11 alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C1-C4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

54. The compound according to claim 52, wherein: R3 is hydrogen, C1-C8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 sulfide, C1-C4 sulfonyl, nitro, carboxylic acid, ester, amine, or C1-C4 alkylamine.

55. The compound according to claim 52, wherein: R4, R4', R5, R5', R7, R7', R8, R8', R9, R9', R10, and R10' are each independently hydrogen, methyl, methyl ester, ethyl ester, C1-C2 amide, carboxylic acid, methoxy, or sulfonamide; R6 is hydrogen or benzimidazole; and m is 1.

56. The compound according to claim 52, wherein R4', R5', R7', R8', R9', and R10' are hydrogen.

57. The compound according to claim 52, wherein R1 is hydrogen.

58. The compound according to claim 52, wherein at least one R4, R4', R8, and R8', are not hydrogen.

59. The compound according to claim 52, wherein at least two R5, R5', R9, and R9', are not hydrogen.

60. The compound according to claim 52, wherein at least one R7, R7', R10, and R10' are not hydrogen.

61. A compound of the formula: ##STR257##

62. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition comprising the compound according to claim 16 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising the compound according to claim 26 and a pharmaceutically acceptable carrier.

65. A pharmaceutical composition comprising the compound according to claim 38 and a pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising the compound according to claim 52 and a pharmaceutically acceptable carrier.

67. A method of treating, preventing, or ameliorating one or more symptoms associated with a respiratory syncytial virus (RSV) infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

68. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered orally, parenterally, transdermally, or mucosally.

69. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the compound is administered in an amount from about 10 mg/kg/day to about 15 mg/kg/day.

70. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the mammal is a human subject.

71. The method of treating, preventing, or ameliorating a viral infection according to claim 67, wherein the human subject is a human infant.

72. A method of inhibiting membrane fusion associated events characteristic of a viral infection in a mammal comprising administering

the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

73. A method of treating, preventing, or ameliorating one or more symptoms associated with a HPIV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 16, 26, 38 or 52 and a pharmaceutically acceptable carrier.

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    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

=> e bray b/in
E1            2     BRAY A T/IN
E2            5     BRAY A V/IN
E3            8 --> BRAY B/IN
E4            5     BRAY B A/IN
E5            1     BRAY B B/IN
E6            3     BRAY B D/IN
E7            1     BRAY B G/IN
E8            1     BRAY B K/IN
E9            4     BRAY B L/IN
E10           3     BRAY B R/IN
E11           6     BRAY C/IN
E12           2     BRAY C A/IN

=> s e3
L12           8 "BRAY B"/IN

=> s l12 and (conjugat? or HR1 or HR2 or heptad)
         49008 CONJUGAT?
           162 HR1
           151 HR2
            61 HEPTAD
L13          4 L12 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)
```

=> d l13,bib,ab,1-4

L13 ANSWER 1 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2005-810532 [82] WPIDS
DNC C2005-249146
TI HIV glycoprotein 41-derived peptide for treating HIV infection comprises amino acid with a protected side chain amine for protecting from reactive functionality and amino acid with unprotected amine for reacting with reactive functionality.
DC A96 B05
IN BRAY, B; ZHANG, H
PA (TRIM-N) TRIMERIS INC
CYC 109
PI WO 2005089796 A1 20050929 (200582)* EN 115
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2005089796 A1 WO 2005-US7486 20050308
PRAI US 2004-553063P 20040315
AB WO2005089796 A UPAB: 20051222
NOVELTY - An isolated HIV glycoprotein(gp)41-derived peptide (I) having amino acid(s) containing side chain amine comprises amino acid(s) (a1) having its side chain amine chemically reacted with chemical protecting agent that protects the amine from chemical reactivity with amine-reactive functionality, and amino acid(s) (a2) having an amine unprotected and free for reacting with amine-reactive functionality; selected from an N-terminal amine and/or a side chain amine.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) method (M) for site-specific chemical modification of HIV glycoprotein (gp)41-derived peptide (I) having at least one amino acid with a side chain amine involving: incorporating into the peptide or its fragment at least one (a1) and at least one (a2), during the peptide synthesis; and

(2) method (M1) for producing a substantially homogeneous **conjugate** of HIV gp41-derived peptide and polymer involving: synthesizing (I) having at least one amino acid with a side chain amine by method (M); and covalently coupling a polymer to (I) by chemically reacting the amine-reactive functionality of the polymer to a free amine group of (I), such that the polymer is covalently coupled only to amino acid(s) having a free amine, and not to amino acid(s) protected by the chemical protecting agent.

ACTIVITY - Anti-HIV.

An HIV gp41-derived peptide-**conjugate** comprising T20 (a peptide derived from **HR2** (**heptad** region 2) of HIV) peptide having a sequence Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe, having protected side chain amines of Lys at positions 18 and 28, and having **conjugated** 2K polyethylene glycol (PEG) site-specifically **conjugated** to the N-terminal amine, was tested for anti-HIV activity, by an in vitro Magi-CCR5 (chemokine receptor 5) infectivity assay, as described in US6258782. T20 showed IC50 of less than 0.02 mu g/ml.

MECHANISM OF ACTION - HIV transmission inhibitor; HIV fusion inhibitor.

USE - For producing a substantially homogeneous **conjugate** of HIV gp41-derived peptide and polymer; useful for the manufacture of a

medicament for treatment of HIV infection (claimed).

ADVANTAGE - The HIV gp41-derived peptides contain site-specific modifications for allowing covalent coupling to the activated polyethylene glycol (PEG) polymer, during the formation of PEGylated peptide, at the desired sites and in desired amount. The peptides contain amino acid(s) having side chain amine chemically protected and amino acid(s) having an unprotected free amine, for protection from coupling and coupling with reactive PEG molecules, respectively; thus provide site-specific PEGylation by reaction only with the unprotected amines, and results in substantially homogeneous **conjugates**. The method avoids the cross-linking of the branched PEG molecule by allowing attachment of selected amines and avoiding attachment to multiple amines. Thus avoids the heterogeneity due to variation in the number and sites of PEG molecules attached, and maintains the pharmacological and/or biological properties of the PEGylated **conjugates** of HIV gp41-derived peptides.
Dwg.0/6

L13 ANSWER 2 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2004-375438 [35] WPIDS
DNC C2004-141075
TI **Conjugate** useful for treating HIV-infected individual, comprises polymer operably bound to not less than two synthetic peptides derived from **heptad** repeat region of HIV gp41 by reactive functionality.
DC A96 B04 D16
IN **BRAY, B**; KANG, M; KINDER, D; LACKEY, J W; TVERMOES, N; ZHANG, H; ZHANG, Y; KANG, M C
PA (BRAY-I) BRAY B; (KANG-I) KANG M; (KIND-I) KINDER D; (LACK-I) LACKEY J W; (TVER-I) TVERMOES N; (TRIM-N) TRIMERIS INC
CYC 103
PI WO 2004029073 A2 20040408 (200435)* EN 79
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
US 2004122214 A1 20040624 (200442)
AU 2003278937 A1 20040419 (200462)
EP 1554306 A2 20050720 (200547) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
BR 2003014707 A 20050726 (200551)
CN 1684972 A 20051019 (200612)
KR 2005046780 A 20050518 (200641)
ADT WO 2004029073 A2 WO 2003-US30285 20030926; US 2004122214 A1 Provisional US 2002-414439P 20020927, US 2003-671282 20030924; AU 2003278937 A1 AU 2003-278937 20030926; EP 1554306 A2 EP 2003-770450 20030926, WO 2003-US30285 20030926; BR 2003014707 A BR 2003-14707 20030926, WO 2003-US30285 20030926; CN 1684972 A CN 2003-823021 20030926; KR 2005046780 A WO 2003-US30285 20030926, KR 2005-704391 20050315
FDT AU 2003278937 A1 Based on WO 2004029073; EP 1554306 A2 Based on WO 2004029073; BR 2003014707 A Based on WO 2004029073; KR 2005046780 A Based on WO 2004029073
PRAI US 2003-671282 20030924; US 2002-414439P 20020927
AB WO2004029073 A UPAB: 20040603
NOVELTY - A **conjugate** (I) comprising a polymer operably bound to not less than 2 synthetic peptides, where each peptide is operably bound to polymer by a reactive functionality, comprises sequence derived from a **heptad** repeat region of HIV gp41, and comprises sequence of not less than 16 amino acids and not more than 60 amino acids, and where (I) has

durability comprising antiviral activity against HIV strains resistant to synthetic peptide alone.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for making (M1) (I), involves reacting a first molecule of synthetic peptide with a polymer in forming an intermediate comprising a first intermediate, where the first molecule of synthetic peptide operably binds to a first reactive functionality of the polymer, and reacting the intermediate comprising the first intermediate with a second molecule of synthetic peptide, where the second molecule of synthetic peptide operably binds to the intermediate comprising the first intermediate by a second reactive functionality of the polymer, in forming (I).

ACTIVITY - Anti-HIV. No supporting data is given.

MECHANISM OF ACTION - Inhibitor of gp41-mediated fusion of HIV-1 to a target cell.

USE - (I) is useful for inhibiting transmission of HIV to a target cell, which involves adding (I) to the virus and the cell. (I) inhibits fusion between the virus and the target cell in inhibiting infection of the cell by the virus. (I) further comprises a carrier. (I) is administered to an HIV-infected individual (claimed).

ADVANTAGE - (I) has the advantage of retaining substantial biological activity such as antiviral activity against HIV, and exhibiting durability as compared to synthetic peptide alone without being a part of (I). (I) increases the biological half-life of the synthetic peptide.

DESCRIPTION OF DRAWING(S) - The figure shows a schematic of HIV-1 gp41 showing the **heptad** repeat 1 (**HR1**) and **HR2** along with other functional regions of gp41.

Dwg.1/3

L13 ANSWER 3 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2004-339372 [31] WPIDS
DNC C2004-128758
TI Pharmaceutical composition used to treat Human Immunodeficiency Virus comprises solution comprising synthetic peptide (Human Immunodeficiency Virus fusion inhibitor) in mixture with polyol.
DC A25 A96 B04
IN **BRAY, B**; DI, J; HEILMAN, D
PA (BRAY-I) BRAY B; (DIJJ-I) DI J; (HEIL-I) HEILMAN D; (TRIM-N) TRIMERIS INC
CYC 103
PI US 2004063637 A1 20040401 (200431)* 36
WO 2004028457 A2 20040408 (200431) EN
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
AU 2003270894 A1 20040419 (200462)
BR 2003014651 A 20050802 (200553)
EP 1583545 A2 20051012 (200567) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
MX 2005003108 A1 20050701 (200628)
US 7045552 B2 20060516 (200633)
KR 2005057329 A 20050616 (200644)
ADT US 2004063637 A1 Provisional US 2002-414441P 20020927, US 2003-663589 20030916; WO 2004028457 A2 WO 2003-US30287 20030926; AU 2003270894 A1 AU 2003-270894 20030926; BR 2003014651 A BR 2003-14651 20030926, WO 2003-US30287 20030926; EP 1583545 A2 EP 2003-752607 20030926, WO 2003-US30287 20030926; MX 2005003108 A1 WO 2003-US30287 20030926, MX 2005-3108 20050322; US 7045552 B2 Provisional US 2002-414441P 20020927, US

2003-663589 20030916; KR 2005057329 A WO 2003-US30287 20030926, KR 2005-704390 20050315

FDT AU 2003270894 A1 Based on WO 2004028457; BR 2003014651 A Based on WO 2004028457; EP 1583545 A2 Based on WO 2004028457; MX 2005003108 A1 Based on WO 2004028457; KR 2005057329 A Based on WO 2004028457

PRAI US 2002-414441P 20020927; US 2003-663589 20030916

AB US2004063637 A UPAB: 20040514

NOVELTY - A pharmaceutical composition comprises solution comprising synthetic peptide (Human Immunodeficiency Virus (HIV) fusion inhibitor) in mixture with polyol. The synthetic peptide is 70-500 mg/ml and the polyol is 5-75 %, by weight.

ACTIVITY - Antiviral.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - Used to treat HIV (claimed).

ADVANTAGE - The invention can be used as an injectable solution, contains HIV fusion inhibitor, and minimizes an injection site reaction.

DESCRIPTION OF DRAWING(S) - The drawing is a schematic of HIV gp41 showing **heptad** repeat 1 region and **heptad** repeat 2 region along with other functional regions of gp41.

Dwg.1/1

L13 ANSWER 4 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2001-425177 [45] WPIDS

DNC C2001-128608

TI Synthesizing large quantities of T-1249 or T-1249-like peptides, comprises using combinations of solid and liquid phase techniques to synthesize and combine groups of specific peptide fragments to yield the T-1249 and T-1249-like peptides.

DC A96 B04

IN ANDERSEN, M; **BRAY, B**; FRIEDRICH, P E; KANG, M; FRIEDRICH, E

PA (TRIM-N) TRIMERIS INC; (ANDE-I) ANDERSEN M; (BRAY-I) BRAY B; (FRIE-I) FRIEDRICH P E; (KANG-I) KANG M

CYC 96

PI WO 2001034635 A2 20010517 (200145)* EN 38

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001041337 A 20010606 (200152)

US 6469136 B1 20021022 (200273)

KR 2002038676 A 20020523 (200274)

US 2003125516 A1 20030703 (200345)

MX 2002000021 A1 20030701 (200366)

JP 2003530311 W 20031014 (200368) 36

BR 2000012249 A 20031111 (200379)

CN 1450906 A 20031022 (200406)

EP 1372686 A2 20040102 (200409) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

US 6767993 B2 20040727 (200449)

EP 1372686 B1 20050202 (200510) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

DE 60017955 E 20050310 (200519)

ES 2236043 T3 20050716 (200549)

DE 60017955 T2 20060112 (200611)

TW 237640 B1 20050811 (200659)

ADT WO 2001034635 A2 WO 2000-US35725 20000705; AU 2001041337 A AU 2001-41337

20000705; US 6469136 B1 US 1999-349205 19990707; KR 2002038676 A KR 2002-700199 20020107; US 2003125516 A1 Div ex US 1999-349205 19990707, US 2002-109748 20020329; MX 2002000021 A1 WO 2000-US35725 20000705, MX 2002-21 20020107; JP 2003530311 W WO 2000-US35725 20000705, JP 2001-537346 20000705; BR 2000012249 A BR 2000-12249 20000705, WO 2000-US35725 20000705; CN 1450906 A CN 2000-812530 20000705; EP 1372686 A2 EP 2000-992116 20000705, WO 2000-US35725 20000705; US 6767993 B2 Div ex US 1999-349205 19990707, US 2002-109748 20020329; EP 1372686 B1 EP 2000-992116 20000705, WO 2000-US35725 20000705; DE 60017955 E DE 2000-00017955 20000705, EP 2000-992116 20000705, WO 2000-US35725 20000705; ES 2236043 T3 EP 2000-992116 20000705; DE 60017955 T2 DE 2000-00017955 20000705, EP 2000-992116 20000705, WO 2000-US35725 20000705; TW 237640 B1 TW 2000-113543 20000805

FDT AU 2001041337 A Based on WO 2001034635; US 2003125516 A1 Div ex US 6469136; MX 2002000021 A1 Based on WO 2001034635; JP 2003530311 W Based on WO 2001034635; BR 2000012249 A Based on WO 2001034635; EP 1372686 A2 Based on WO 2001034635; US 6767993 B2 Div ex US 6469136; EP 1372686 B1 Based on WO 2001034635; DE 60017955 E Based on EP 1372686, Based on WO 2001034635; ES 2236043 T3 Based on EP 1372686; DE 60017955 T2 Based on EP 1372686, Based on WO 2001034635

PRAI US 1999-349205 19990707; US 2002-109748 20020329

AB WO 200134635 A UPAB: 20010813

NOVELTY - New method (M1) for synthesizing T-1249 and T-1249-like peptides comprises synthesizing specific side-chain protected peptide fragment intermediates of T-1249 or a T-1249-like peptide on a solid support, coupling the protected fragments in solution to form a protected T-1249 or a T-1249-like peptide, followed by deprotection of the side chains to yield the final T-1249 or a T-1249-like peptide.

DETAILED DESCRIPTION - New method (M1) for synthesizing T-1249 and T-1249-like peptides comprises synthesizing specific side-chain protected peptide fragment intermediates of T-1249 or a T-1249-like peptide on a solid support, coupling the protected fragments in solution to form a protected T-1249 or a T-1249-like peptide, followed by deprotection of the side chains to yield the final T-1249 or a T-1249-like peptide.

The T-1249 peptide has the following sequence:

X-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-Z (S1).

The side chain protected peptides have the following sequence:

(a) EQAQIQQEKNEYELQKLDKWASLWEWF-Z (the amino acid sequence without Z is referred to as S6), where the amino terminus is deprotected; and

(b) X-WQEWEQKITALL-COOH (the amino acid sequence without X is referred to as S2),

where

X = is a protecting group, an acetyl group or a macromolecular carrier group; and

Z = is a protecting group, an amido group, or a macromolecular carrier group.

INDEPENDENT CLAIMS are also included for the following:

(1) a set of peptide fragments comprising a set selected from:

(a) S2, EQAQIQQEKNEYEL (S3) and QKLDKWASLWEW (S4);

(b) S2, S3 and QKLDKWASLWEWF (S5);

(c) S2 and S6;

(d) S2 and EQAQIQQEKNEYELQKLDKWASLWEW (S8);

(e) WQEWEQKITALLEQAQIIQQEKNEYEL (S7) and S4; or

(f) S7 and S5; and

(2) a peptide selected from S2, S3, S4, S5, S6, S7 or S8.

USE - The method is useful for producing large quantities of T-1249 and T-1249-like peptides.

ADVANTAGE - The T-1249 and T-1249-like peptides may be synthesized on a scale of one or more kilograms. The method uses only about a 0.5-fold excess (about 1.5 equivalents) of amino acid in the solid phase synthesis of the peptide fragments. This reduction in the amount of amino acid and reagents makes the method suitable for large scale synthesis of T-1249 and

T-1249-like peptides. Synthesizing the selected peptide fragments in the solid phase using super acid sensitive resin produces peptide fragments of unusually high purity. Chromatographic techniques are not necessary to purify the peptide fragments produced. Use of a super acid sensitive resin allows the synthesized, protected peptides to be cleaved from the resin without concomitant removal of the side-chain protecting groups. This reduces impurities, and allows peptides comprising 10 amino acids or greater to be synthesized in high purity and yield.
Dwg.0/1

```
=> e lackey j w/in
E1            1     LACKEY J P/IN
E2            2     LACKEY J R/IN
E3            9 --> LACKEY J W/IN
E4            2     LACKEY K/IN
E5           17     LACKEY K E/IN
E6            2     LACKEY K R/IN
E7            5     LACKEY L/IN
E8            2     LACKEY L D/IN
E9            1     LACKEY M/IN
E10           2     LACKEY M B/IN
E11           1     LACKEY M D/IN
E12           1     LACKEY M E/IN

=> s e3
L14           9 "LACKEY J W"/IN

=> s l14 not l13
L15           8 L14 NOT L13

=> s l15 and (conjugat? or HR1 or HR2 or heptad)
         49008 CONJUGAT?
           162 HR1
           151 HR2
            61 HEPTAD
L16           0 L15 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)

=> file medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              24.12      65.48

FILE 'MEDLINE' ENTERED AT 05:24:07 ON 02 OCT 2006

 FILE LAST UPDATED: 30 Sep 2006 (20060930/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.
```

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> e bray b/au
E1            1      BRAY ANDREA/AU
E2            5      BRAY ANDREW M/AU
E3           15 --> BRAY B/AU
E4           21      BRAY B A/AU
E5           14      BRAY B E/AU
E6            7      BRAY B J/AU
E7            6      BRAY B M/AU
E8            1      BRAY B V/AU
E9            1      BRAY BARBARA/AU
E10           1      BRAY BENJAMIN D/AU
E11           1      BRAY BETHANY CARA/AU
E12           2      BRAY BRIAN/AU

=> s e12
L17           2 "BRAY BRIAN"/AU

=> d l17,cbib,ab,1-2

L17  ANSWER 1 OF 2     MEDLINE on STN
2006540506.     PubMed ID: 16767741.   Second virial coefficient determination
     of a therapeutic peptide by self-interaction chromatography. Payne Robert
     W; Nayar Rajiv; Tarantino Ralph; Terzo Sam Del; Moschera John; Di Jie;
     Heilman David; Bray Brian; Manning Mark Cornell; Henry Charles S.
     (Department of Chemistry, Colorado State University, Fort Collins, CO. )
     Biopolymers, (2006) Vol. 84, No. 5, pp. 527-33.  Journal code: 0372525.
     ISSN: 0006-3525. Pub. country: United States. Language: English.
AB   Self-interaction of macromolecules has been shown to play an important
     role in a number of physical processes, including crystallization,
     solubility, viscosity, and aggregation.  Peptide self-interaction is not
     as well studied as for larger proteins, but should play an equally
     important role.  The osmotic second virial coefficient, B, can be used to
     quantify peptide and protein self-interaction.  B values are typically
     measured using static light scattering (SLS).  Peptides, however, do not
     scatter enough light to allow such measurements.  This study describes the
     first use of self-interaction chromatography (SIC) for the measurement of
     peptide B values because SIC does not have the molecular size limitations
     of SLS.  In the present work, SIC was used to measure B for enfuvirtide, a
     36-amino acid therapeutic peptide, as a function of salt concentration,
     salt type, and pH.  B was found to correlate strongly with solubility and
     apparent molecular weight.  In general, the solubility of enfuvirtide
     increases with pH from 6 to 10 and decreases as the salt concentration
     increases from 0 to 0.5M for three different salts.  The effect of peptide
     concentration on B was also investigated and shown to have a significant
     effect, but only at high concentrations (>80 mg/mL).  (c) 2006 Wiley
     Periodicals, Inc.  Biopolymers (Pept Sci) 84: 527-533, 2006.

L17  ANSWER 2 OF 2     MEDLINE on STN
2004167649.     PubMed ID: 15061528.   The PICNIC approach to regional care
     networks.  Bray Brian.  (PICNIC project, Minoru Development Corporation,
     Paris, France.. brianbr@openhealth.com) .  Studies in health technology and
     informatics, (2003) Vol. 96, pp. 80-7.  Ref: 7.  Journal code: 9214582.
     ISSN: 0926-9630. Pub. country: Netherlands. Language: English.
AB   PICNIC is a pioneering project to develop an architecture for next
     generation regional healthcare networks.  This paper gives an overview of
     the project and some of the reasoning behind the interrelated technical
     and business choices.
```

```
=> e bray b/au
E1            1      BRAY ANDREA/AU
E2            5      BRAY ANDREW M/AU
E3           15 --> BRAY B/AU
E4           21      BRAY B A/AU
E5           14      BRAY B E/AU
E6            7      BRAY B J/AU
E7            6      BRAY B M/AU
E8            1      BRAY B V/AU
E9            1      BRAY BARBARA/AU
E10           1      BRAY BENJAMIN D/AU
E11           1      BRAY BETHANY CARA/AU
E12           2      BRAY BRIAN/AU

=> s e3
L18          15 "BRAY B"/AU

=> s l18 and (conjugat? or HR1 or HR2 or heptad)
         82786 CONJUGAT?
           250 HR1
           202 HR2
           949 HEPTAD
L19          0 L18 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)

=> e lackey j w/au
E1            1      LACKEY J O/AU
E2            3      LACKEY J T/AU
E3            0 --> LACKEY J W/AU
E4            1      LACKEY JAMIE/AU
E5            1      LACKEY JEFFREY N/AU
E6            1      LACKEY JOANNE/AU
E7            1      LACKEY JODI J/AU
E8            9      LACKEY K/AU
E9            1      LACKEY K E/AU
E10           1      LACKEY K L/AU
E11           9      LACKEY KAREN/AU
E12           4      LACKEY KAREN E/AU

=> d his

     (FILE 'HOME' ENTERED AT 05:19:18 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 05:19:28 ON 02 OCT 2006
                E BRAY BRIAN/IN
L1           13 S E3-E5
L2            6 S L1 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3            6 S L2 AND (CONJUGATE? OR HR1 OR HR2 OR HEPTAD)
                E KANG MYUNG CHOI/IN
L4            5 S E4
L5            0 S L4 NOT L1
                E TVERMOES NICOLAI/IN
L6            3 S E3-E4
L7            2 S L6 NOT L1
                E KINDER DANIEL/IN
L8            5 S E3-E5
L9            4 S L8 NOT L1
                E LACKEY JOHN W/IN
L10          10 S E3 OR E4
L11           5 S L10 AND (CONJUGAT? OR HEPTAD OR HR1 OR HR2)

     FILE 'WPIDS' ENTERED AT 05:22:42 ON 02 OCT 2006
```

```
                E BRAY B/IN
L12             8 S E3
L13             4 S L12 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)
                E LACKEY J W/IN
L14             9 S E3
L15             8 S L14 NOT L13
L16             0 S L15 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)

     FILE 'MEDLINE' ENTERED AT 05:24:07 ON 02 OCT 2006
                E BRAY B/AU
L17             2 S E12
                E BRAY B/AU
L18            15 S E3
L19             0 S L18 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)
                E LACKEY J W/AU

=> file usptaful
'USPTAFUL' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'MEDLINE'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.

=> file uspatful
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 1.22      66.70

FILE 'USPATFULL' ENTERED AT 05:25:29 ON 02 OCT 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Sep 2006 (20060928/PD)
FILE LAST UPDATED: 28 Sep 2006 (20060928/ED)
HIGHEST GRANTED PATENT NUMBER: US7114185
HIGHEST APPLICATION PUBLICATION NUMBER: US2006218687
CA INDEXING IS CURRENT THROUGH 28 Sep 2006 (20060928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Sep 2006 (20060928/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006


=> s (HIV or human immunodeficiency virus)
         45383 HIV
        522505 HUMAN
         25660 IMMUNODEFICIENCY
        105701 VIRUS
         18282 HUMAN IMMUNODEFICIENCY VIRUS
                  (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L20      47774 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l20 and (HR1 or HR2 or heptad)
           521 HR1
           432 HR2
           842 HEPTAD
L21        537 L20 AND (HR1 OR HR2 OR HEPTAD)

=> s l21 and conjugat?
        163821 CONJUGAT?
L22        439 L21 AND CONJUGAT?

=> s l22 and (PEG? or polyethylene glycol)
```

```
         94562 PEG?
        451621 POLYETHYLENE
        336914 GLYCOL
        151113 POLYETHYLENE GLYCOL
                 (POLYETHYLENE(W)GLYCOL)
L23        305 L22 AND (PEG? OR POLYETHYLENE GLYCOL)

=> s l23 and (conjugat?/clm)
         29821 CONJUGAT?/CLM
L24         29 L23 AND (CONJUGAT?/CLM)

=> d his

     (FILE 'HOME' ENTERED AT 05:19:18 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 05:19:28 ON 02 OCT 2006
                E BRAY BRIAN/IN
L1           13 S E3-E5
L2            6 S L1 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3            6 S L2 AND (CONJUGATE? OR HR1 OR HR2 OR HEPTAD)
                E KANG MYUNG CHOI/IN
L4            5 S E4
L5            0 S L4 NOT L1
                E TVERMOES NICOLAI/IN
L6            3 S E3-E4
L7            2 S L6 NOT L1
                E KINDER DANIEL/IN
L8            5 S E3-E5
L9            4 S L8 NOT L1
                E LACKEY JOHN W/IN
L10          10 S E3 OR E4
L11           5 S L10 AND (CONJUGAT? OR HEPTAD OR HR1 OR HR2)

     FILE 'WPIDS' ENTERED AT 05:22:42 ON 02 OCT 2006
                E BRAY B/IN
L12           8 S E3
L13           4 S L12 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)
                E LACKEY J W/IN
L14           9 S E3
L15           8 S L14 NOT L13
L16           0 S L15 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)

     FILE 'MEDLINE' ENTERED AT 05:24:07 ON 02 OCT 2006
                E BRAY B/AU
L17           2 S E12
                E BRAY B/AU
L18          15 S E3
L19           0 S L18 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)
                E LACKEY J W/AU

     FILE 'USPATFULL' ENTERED AT 05:25:29 ON 02 OCT 2006
L20       47774 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21         537 S L20 AND (HR1 OR HR2 OR HEPTAD)
L22         439 S L21 AND CONJUGAT?
L23         305 S L22 AND (PEG? OR POLYETHYLENE GLYCOL)
L24          29 S L23 AND (CONJUGAT?/CLM)

=> s l24 not l1
L25         28 L24 NOT L1

=> s l25 ay<2004
MISSING OPERATOR L25 AY<2004
```

The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l25 and ay<2004
4094073 AY<2004
L26 25 L25 AND AY<2004

=> d l26,cbib,clm,1-25

L26 ANSWER 1 OF 25 USPATFULL on STN
2004:301902 Methods for inhibition of membrane fusion-associated events, including **HIV** transmission.
Bolognesi, Dani Paul, Durham, NC, United States
Matthews, Thomas James, Durham, NC, United States
Wild, Carl T., Durham, NC, United States
Duke University, Durham, NC, United States (U.S. corporation)
US 6824783 B1 20041130
APPLICATION: US 1995-487266 19950607 (8)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for the inhibition of transmission of **HIV**-1 to a cell, comprising contacting the virus, in the presence of the cell, with an effective concentration of a peptide for an effective period of time, so that infection of the cell by the virus is inhibited, wherein the peptide has the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

2. The method of claim 1, wherein X is an acetyl group, and Z is an amido group.

3. The method of claim 1, wherein X is an amino group.

4. The method of claim 1, wherein Z is a carboxyl group.

5. The method of claim 1, wherein X is a 9-fluorenylmethoxy-carbonyl group.

6. A method for inhibiting **HIV**-1 infection of a cell, comprising contacting the virus, in the presence of the cell, for an effective period of time with an effective amount of a peptide having the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

7. A method for treating or delaying the onset of AIDS in an **HIV**-1 infected individual, comprising administering to the individual an effective amount of a peptide having the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

8. A method for increasing the number of CD4- cells in an **HIV**-1 infected individual, comprising administering to the individual an effective amount of a peptide having the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

9. A method for lowering plasma levels of **HIV**-1 in an individual, comprising administering to the individual an effective amount of a peptide having the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

10. The method of claim 6, wherein X is a hydrophobic group.

11. The method of claim 10, wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

12. The method of claim 6, wherein Z is a hydrophobic group.

13. The method of claim 12, wherein the hydrophobic group Z is t-butyloxycarbonyl.

14. The method of claim 6, wherein X is a macromolecular carrier group.

15. The method of claim 14, wherein the macromolecular carrier group X is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

16. The method of claim 6, wherein Z is a macromolecular carrier group.

17. The method of claim 16, wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

18. The method of claim 6, wherein at least one bond linking adjacent amino acid residues of the peptide is a non-peptide bond.

19. The method of claim 18, wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

20. The method of claim 6, wherein at least one amino acid residue of the peptide is in a D-isomer configuration.

21. The method of claim 6, wherein X is an acetyl group, and Z is an amido group.

22. The method of claim 14, wherein the macromolecular carrier group X is a peptide group.

23. The method of claim 16, wherein the macromolecular carrier group Z is a peptide group.

24. The method of claim 23, wherein X is a peptide macromolecular carrier group and Z is a peptide macromolecular carrier group.

25. The method of claim 6, wherein X is an amino group.

26. The method of claim 6, wherein Z is a carboxyl group.

27. The method of claim 6, wherein X is a 9-fluorenylmethoxy-carbonyl group.

28. The method of claim 6, further comprising contacting the virus with a pharmaceutically acceptable carrier.

29. The method of claim 7, wherein X is a hydrophobic group.

30. The method of claim 29, wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

31. The method of claim 7, wherein Z is a hydrophobic group.

32. The method of claim 31, wherein the hydrophobic group Z is t-butyloxycarbonyl.

33. The method of claim 7, wherein X is a macromolecular carrier group.

34. The method of claim 33, wherein the macromolecular carrier group X is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

35. The method of claim 7, wherein Z is a macromolecular carrier group.

36. The method of claim 35, wherein th e macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

37. The method of claim 7, wherein at least one bond linking adjacent amino acid residues of the peptide is a non-peptide bond.

38. The method of claim 37, wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

39. The method of claim 7, wherein at least one amino acid residue of the peptide is in a D-isomer configuration.

40. The method of claim 7, wherein X is an acetyl group, and Z is an amido group.

41. The method of claim 33, wherein the macromolecular carrier group X is a peptide group.

42. The method of claim 35, wherein the macromolecular carrier group Z is a peptide group.

43. The method of claim 42, wherein X is a peptide macromolecular carrier group and Z is a peptide macromolecular carrier group.

44. The method of claim 7, wherein X is an amino group.

45. The method of claim 7, wherein Z is a carboxyl group.

46. The method of claim 7, wherein X is a 9-fluorenylmethoxy-carbonyl group.

47. The method of claim 8, further comprising administering to the individual a pharmaceutically acceptable carrier.

48. The method of claim 8, wherein X is a hydrophobic group.

49. The method of claim 48, wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

50. The method of claim 8, wherein Z is a hydrophobic group.

51. The method of claim 50, wherein the hydrophobic group Z is t-butyloxycarbonyl.

52. The method of claim 8, wherein X is a macromolecular carrier group.

53. The method of claim 52, wherein the macromolecular carrier group X is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

54. The method of claim 8, wherein Z is a macromolecular carrier group.

55. The method of claim 54, wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

56. The method of claim 8, wherein at least one bond linking adjacent amino acid residues of the peptide is a non-peptide bond.

57. The method of claim 56, wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

58. The method of claim 8, wherein at least one amino acid residue of the peptide is in a D-isomer configuration.

59. The method of claim 8, wherein X is an acetyl group, and Z is an amido group.

60. The method of claim 52, wherein the macromolecular carrier group X is a peptide group.

61. The method of claim 54, wherein the macromolecular carrier group Z is a peptide group.

62. The method of claim 61, wherein X is a peptide macromolecular carrier group and Z is a peptide macromolecular carrier group.

63. The method of claim 8, wherein X is an amino group.

64. The method of claim 8, wherein Z is a carboxyl group.

65. The method of claim 8, wherein X is a 9-fluorenylmethoxy-carbonyl group.

66. The method of claim 9, further comprising administering to the patient a pharmaceutically acceptable carrier.

67. The method of claim 9, wherein X is a hydrophobic group.

68. The method of claim 67, wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

69. The method of claim 9, wherein Z is a hydrophobic group.

70. The method of claim 69, wherein the hydrophobic group Z is

t-butyloxycarbonyl.

71. The method of claim 9, wherein X is a macromolecular carrier group.

72. The method of claim 71, wherein the macromolecular carrier group X is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

73. The method of claim 9, wherein Z is a macromolecular carrier group.

74. The method of claim 73, wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

75. The method of claim 9, wherein at least one bond linking adjacent amino acid residues of the peptide is a non-peptide bond.

76. The method of claim 75, wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

77. The method of claim 9, wherein at least one amino acid residue of the peptide is in a D-isomer configuration.

78. The method of claim 9, wherein X is an acetyl group, and Z is an amido group.

79. The method of claim 71, wherein the macromolecular carrier group X is a peptide group.

80. The method of claim 73, wherein the macromolecular carrier group Z is a peptide group.

81. The method of claim 80, wherein X is a peptide macromolecular carrier group and Z is a peptide macromolecular carrier group.

82. The method of claim 9, wherein X is an amino group.

83. The method of claim 9, wherein Z is a carboxyl group.

84. The method of claim 9, wherein X is a 9-fluorenylmethoxy-carbonyl group.

85. The method of claim 1, wherein X is a hydrophobic group.

86. The method of claim 85, wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

87. The method of claim 1, wherein Z is a hydrophobic group.

88. The method of claim 87, wherein the hydrophobic group Z is t-butyloxycarbonyl.

89. The method of claim 1, wherein X is a macromolecular carrier group.

90. The method of claim 89, wherein the macromolecular carrier group X is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety, or a peptide group.

91. The method of claim 1, wherein Z is a macromolecular carrier group.

92. The method of claim 91, wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a

carbohydrate moiety, or a peptide group.

93. The method of claim 1, wherein at least one bond linking adjacent amino acid residues of the peptide is a non-peptide bond.

94. The method of claim 93, wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

95. The method of claim 1, wherein at least one amino acid residue of the peptide is in a D-isomer configuration.

96. The method of claim 1, wherein X is a peptide macromolecular carrier group.

97. The method of claim 1, wherein Z is a peptide macromolecular carrier group.

98. The method of claim 1, wherein X is a peptide macromolecular carrier group X , and further wherein Z is a peptide macromolecular carrier group.

99. The method of claim 7, further comprising administering to the individual a pharmaceutically acceptable carrier.

100. A method for inhibiting syncytia formation between **HIV-1** infected cells and cells uninfected by **HIV-1**, comprising contacting the infected cells for an effective period of time with an effective amount of a peptide having the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ ID NO:1); in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

101. The method of claim 100, wherein X is a hydrophobic group.

102. The method of claim 101, wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

103. The method of claim 100, wherein Z is a hydrophobic group.

104. The method of claim 103, wherein the hydrophobic group Z is t-butyloxycarbonyl.

105. The method of claim 100, wherein X is a macromolecular carrier group.

106. The method of claim 106, wherein the macromolecular carrier group X is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

107. The method of claim 100, wherein Z is a macromolecular carrier group.

108. The method of claim 108, wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

109. The method of claim 100, wherein at least one bond linking adjacent amino acid residues of the peptide is a non-peptide bond.

110. The method of claim 110, wherein the non-peptide bond is an imino,

ester, hydrazine, semicarbazide, or azo bond.

111. The method of claim 100, wherein at least one amino acid residue of the peptide is in a D-isomer configuration.

112. The method of claim 100, wherein X is an acetyl group, and Z is an amido group.

113. The method of claim 100, wherein X is a peptide macromolecular carrier group.

114. The method of claim 100, wherein Z is a peptide macromolecular carrier group.

115. The method of claim 100, wherein X is a peptide macromolecular carrier group and Z is a peptide macromolecular carrier group.

116. The method of claim 100, wherein X is an amino group.

117. The method of claim 100, wherein Z is a carboxyl group.

118. The method of claim 100, wherein X is a 9-fluorenylmethoxy-carbonyl group.

L26 ANSWER 2 OF 25 USPATFULL on STN
2004:273309 Methods of eliciting broadly neutralizing antibodies targeting **HIV**-1 gp41.
Wild, Carl T., Gaithersburg, MD, UNITED STATES
Weiss, Carol D., Bethesda, MD, UNITED STATES
Panacos Pharmaceuticals, Inc., Gaithersburg, MD, UNITED STATES, 20877 (U.S. corporation)
US 2004213801 A1 20041028
APPLICATION: US 2003-660206 A1 20030910 (10)
PRIORITY: US 1999-115404P 19990108 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1-24. (canceled)

25. A **conjugate** peptide or polypeptide formed from two or more amino acid sequences that comprise: (a) one or more amino acid sequences that are capable of forming a stable coiled-coil solution structure corresponding to or mimicking the **heptad** repeat region of gp41 (N-helical domain); and (b) one or more amino acid sequences that correspond to, or mimic, an amino acid sequence of the transmembrane proximal amphipathic α-helical segment of gp41 (C-helical domain); wherein said one or more sequences (a) and (b) are alternately linked to one another via a bond, such as a peptide bond (amide linkage) or by an amino acid linking sequence consisting of about 2 to about 25 amino acids.

26. The **conjugate** of claim 25, wherein: said N-helical peptide comprises about 28 to 55 amino acids of the following sequence: ARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGI (SEQ. ID NO: 1), or multimers thereof; and said C-helical peptide comprises about 24-56 amino acids of the following sequence: WNNMTWMEWDREINNYTSLIHSLIEESQNQQE KNEQELLELDKWASLWNWFNI TNW (SEQ ID NO:4), or multimers thereof.

27. The **conjugate** of claim 25, wherein: said N-helical peptide is one of SEQ ID NO: I SEQ ID NO: 2, SEQ ID NO: 3, or one of SEQ ID NO: 9 through SEQ ID NO: 40, and wherein the peptide can be optionally coupled

to a larger carrier protein, or optionally include a terminal protecting group at the N- and/or C-termini, and said C-helical peptide is one of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or one of SEQ ID NO: 41 through SEQ ID NO: 74, and wherein the peptide can be optionally coupled to a larger carrier protein, or optionally include a tensional protecting group at the N- and/or C-termini.

28. A pharmaceutical composition comprising a **conjugate** of claim 25, and a pharmaceutical acceptable carrier.

29. A composition comprising polyclonal or monoclonal antibodies that are raised to the **conjugate** of claim 25.

30. A composition comprising a mixture of C-helical peptide or polypeptide and N-helical peptide or polypeptide, wherein said mixture forms a stable core helix solution structure.

31. The composition of claim 30, wherein: said N-helical peptide comprises about 28 to 55 ammo acids of the following sequence: ARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGI (SEQ. ID NO: 1), or multimers thereof; and said C-helical peptide comprises about 24-56 amino acids of the following sequence: WNNMTWMEWDREINNYTSLIHSLIEESQNQQE KNEQELLELDKWASLWNWFNI TNW (SEQ ID NO:4), or multimers thereof.

32. The composition of claim 30, wherein: said N-helical peptide is one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or one of SEQ ID NO: 9 through SEQ ID NO: 40, and wherein the peptide can be optionally coupled to a larger carrier protein, or optionally include a terminal protecting group at the N- and/or C-termini; and said C-helical peptide is one of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or one of SEQ ID NO: 41 through SEQ ID NO: 74, and wherein the peptide can be optionally coupled to a larger carrier protein, or optionally include a terminal protecting group at the N- and/or C-termini.

33. A composition comprising polyclonal or monoclonal antibodies that are raised to the composition of claim 30.

34. A method of treatment, comprising: administering to an individual a composition comprising polyclonal or monoclonal antibodies as claimed in claim 29 or claim 33 in an amount effective to reduce **HIV** infection of uninfected cells.

35. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence encoding a peptide or polypeptide **conjugate** of claim 25.

36. The nucleic acid molecule of claim 357 wherein said polynucleotide has the nucleotide sequence in FIG. 7.

37. A method for making a recombinant vector comprising inserting an isolated nucleic acid molecule of claim 35 into a vector.

38. A recombinant vector produced by the method of claim 37.

39. A method of making a recombinant host cell comprising introducing the recombinant vector of claim 38 into a host cell.

40. A recombinant host cell produced by the method of claim 39.

41. A recombinant method for producing a **conjugate** peptide or polypeptide, comprising culturing the recombinant host cell of claim 40 under conditions such tat said polypeptide is expressed and recovering

said polypeptide.

42. The method of claim 1, claim 8, claim 15 or claim 20, wherein said administering is provided in advance of any symptoms of **HIV** infection, or in advance of any known exposure to **HIV**.

43. The method of claim 1, claim 8, claim 15 or claim 20, wherein said administering is provided upon or after the detection of symptoms which indicate that an animal may be infected with **HIV**, or upon or after exposure to the virus.

44. A method of raising a broadly neutralizing antibody response to **HIV** comprising: administering to a mammal a peptide or polypeptide wherein said peptide or polypeptide comprises: i) SEQ ID NO:2, SEQ ID NO:3, or one of SEQ ID NO:9 through SEQ ID NO: 40; or ii) a peptide having 1 to 10 conservative amino acid substitutions of SEQ ID NO:2, SEQ ID NO:3, or one of SEQ ID NO:9 through SEQ ID NO:40.

45. The method of claim 44, wherein said peptide or polypeptide is coupled to a terminal protecting group at the N- and/or C-termini.

46. The method of claim 44, wherein said peptide or polypeptide comprises SEQ ID NO:2 or SEQ ID NO:3.

47. The method of claim 44, wherein said peptide or polypeptide is **conjugated** to a carrier protein.

48. The method of claim 47, wherein said carrier protein is keyhole limpet hemocyanin (KLH), ovalbumin, bovine serum albumin (BSA) or tetanus toxoid.

49. A method of raising a broadly neutralizing antibody response to **HIV** comprising: administering to a mammal a peptide or polypeptide wherein said peptide or polypeptide comprises: i) SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:77, or one of SEQ ID NO:41 through SEQ ID NO: 74; or ii) a peptide having 1 to 10 conservative amino acid substitutions of SEQ ID NO:5, SEQ ID NO:6, or one of SEQ ID NO:41 rough SEQ ID NO:74.

50. The method of claim 49, wherein a peptide is administered, and wherein said peptide comprises SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:77.

51. The method of claim 49, wherein said peptide or polypeptide is coupled to a terminal protecting group at the N- and/or C-termini.

52. The method of claim 49, wherein said peptide or polypeptide comprises SEQ ID NO:5.

53. The method of claim 49, wherein said peptide or polypeptide is **conjugated** to a carrier protein.

54. The method of claim 53, wherein said carrier protein is keyhole limpet hemocyanin (KLH), ovalbumin, bovine serum albumin (BSA) or tetanus toxoid.

55. A method of raising a broadly neutralizing antibody response to **HIV** comprising: administering to a mammal a composition including at least two peptides or polypeptides, wherein said peptides or polypeptides comprise SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:3 and SEQ ID NO.6, SEQ ID NO:2 and SEQ ID NO:6, or SEQ ID NO:3 and SEQ ID NO:5.

56. The method of claim 55, wherein peptides or polypeptides form a

stable six helix bundle structure.

57. A method of raising a broadly neutralizing antibody response to **HIV** comprising: administering to a mammal a composition including at least one **conjugate** peptides or polypeptides formed from two or more amino acid sequences that comprise: i) one or more amino acid sequence SEQ ID NO:2, SEQ ID NO:3, or one of SEQ ID NO:9 through SEQ ID NO:40 or peptides having 1 to 10 conservative amino acid substitutions of each sequence; and ii) one or more amino acid sequence SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, or one of SEQ ID NO:41 through SEQ ID NO:74 or a peptide having 1 to 10 conservative amino acid substitutions of each sequence; wherein, said one or more sequences (i) and (ii) are alternatively linked to one another via a bond, such as a peptide bond (amide linkage) or by an amino acid ling sequence consisting of about 2 to about 25 amino acids.

58. A method of claim 57, wherein said amino acid ling sequence is of a $(GGGGS)_3$ motif (SEQ ID NO:7).

59. The method of claim 57, wherein sequence a) comprises SEQ ID NO:2 or 3 and sequence b) comprises SEQ ID NO:5 or SEQ ID NO:6.

60. The method of claim 59, wherein the sequence of (a) is linked to a sequence of (b) is linked to (a) sequence.

61. The method of claim 59, wherein a sequence of (b) is linked to a sequence of (a) is linked to a sequence of (b).

62. The method of claim 59, wherein said one or more sequences is one of (a) and (b), and wherein said peptides are coupled to a larger carrier protein.

L26 ANSWER 3 OF 25 USPATFULL on STN
2004:178985 Devices containing DNA encoding neurotrophic agents and related compositions and methods.
Baird, Andrew, London, UNITED KINGDOM
Gonzalez, Ana Maria, San Diego, CA, UNITED STATES
Logan, Ann, Stourport on Severn, UNITED KINGDOM
Berry, Martin, Edgbaston, UNITED KINGDOM
Selective Genetics, Inc., San Diego, CA (non-U.S. corporation)University of Birmingham, Edgbaston, UNITED KINGDOM (non-U.S. corporation)King's College, London, UNITED KINGDOM (non-U.S. corporation)
US 2004138155 A1 20040715
APPLICATION: US 2003-348051 A1 20030117 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A device for promoting neuronal regeneration, comprising: a gene activated matrix comprising a biocompatible matrix and at least one neuronal therapeutic encoding agent having an operably linked promoter.

2. A device for promoting neuronal survival, comprising: a gene activated matrix comprising a biocompatible matrix and at least one neuronal therapeutic encoding agent having an operably linked promoter.

3. The device of either claim 1 or claim 2 wherein the promoter is an inducible promoter.

4. The device of either claim 1 or claim 2 wherein the promoter is a tissue specific promoter.

5. The device of either claim 1 or claim 2 wherein the promoter is selected from the group consisting of GAP43 promoter, GFAP promoter, neuron specific enolase promoter, FGF-receptor promoter, elastase I gene control region, immunoglobulin gene control region, alpha-1-antitrypsin gene control region, beta-globin gene control region, myelin basic protein gene control region, myosin light chain 2 gene control region, RSV promoter, vaccinia virus 7.5K promoter, SV40 promoter, HSV promoter, MLP adenovirus promoter, MMTV LTR promoter, CMV promoter, metallothionein promoter, a promoter having at least one cAMP response element, tie promoter, VCAM-1 promoter, alpha V-beta 3 integrin promoters, ICAM-3 promoter, CD44 promoter, CD40 promoter, notch 4 promoter, and an event type-specific promoter.

6. The device of either claim 1 or claim 2 wherein the promoter is a neuronal cell specific promoter.

7. The device of claim 6 wherein the promoter is selected from the group consisting of GAP43 promoter, FGF receptor promoter and neuron specific enolase promoter.

8. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent encodes a neurotrophic factor.

9. The device of claim 8 wherein the neurotrophic factor is a member of the neurotrophin family.

10. The device of claim 8 wherein the neurotrophic factor is a member of the FGF family.

11. The device of claim 8 wherein the neurotrophic factor is selected from the group consisting of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), cardiotrophin-1 (CT-1), choline acetyltransferase development factor (CDF), ciliary neurotrophic factor (CNTF), oncostatin M (OSM); fibroblast growth factor-1 (FGF-1), FGF-2, FGF-5, glial cell-line-derived neurotrophic factor (GDNF), insulin, insulin-like growth factor-1 (IGF-1), IGF-2, interleukin-6 (IL-6), leukemia inhibitor factor (LIF), neurite promoting factor (NPF), neurotrophin-3 (NT-3), NT-4, platelet-derived growth factor (PDGF), protease nexin-1 (PN-1), S-100, transforming growth factor-β (TGF-β), and vasoactive intestinal peptide (VIP).

12. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent encodes an inhibitor of an antagonist of axonal generation or regeneration.

13. The device of claim 12 wherein the inhibitor of an antagonist of axonal generation or regeneration is an inhibitor of TGF-beta.

14. The device of claim 13 wherein the inhibitor of TGF-beta is selected from the group consisting of decorin, a TGF-beta inhibitory chemokine, an anti-TGF-beta antibody, an antisense TGF-beta oligonucleotide, a TGF-beta gene specific ribozyme and a mutated TGF-beta.

15. The device of claim 14 wherein the TGF-beta inhibitory chemokine is an ELR containing member of the CXC chemokine family.

16. The device of claim 15 wherein the ELR containing member of the CXC chemokine family is selected from the group consisting of interleukin-8, ENA-78, GROα, GROβand GROγ.

17. The device of claim 13 wherein the inhibitor of TGF-beta is decorin.

18. The device of claim 13 wherein the inhibitor of TGF-beta is an anti-TGF-beta antibody.

19. The device of claim 13 wherein the inhibitor of TGF-beta is a mutated TGF-beta.

20. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent is non-covalently associated with the gene activated matrix.

21. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent is adsorbed to the gene activated matrix.

22. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent is absorbed in the gene activated matrix.

23. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent is capable of inducing neuronal axonal generation or regeneration.

24. A device for promoting neuronal regeneration, comprising: a gene activated matrix; at least one support cell; and at least one neuronal therapeutic encoding agent having an operably linked promoter.

25. A device for promoting neuronal survival, comprising: a gene activated matrix; at least one support cell; and at least one neuronal therapeutic encoding agent having an operably linked promoter.

26. The device of either claim 24 or claim 25 wherein the support cell is a Schwann cell.

27. The device of either claim 24 or claim 25 wherein the support cell is an oligodendrocyte.

28. The device of either claim 24 or claim 25 wherein the support cell is an astrocyte.

29. The device of either claim 24 or claim 25 wherein the support cell is a microglial cell.

30. The device of either claim 24 or claim 25 wherein the support cell is a fibroblast.

31. The device of either claim 24 or claim 25 wherein the support cell is a macrophage.

32. The device of either claim 24 or claim 25 wherein the support cell is an inflammatory cell selected from the group consisting of a macrophage, a neutrophil, a monocyte, a granulocyte and a lymphocyte.

33. The device of any one of claims 1, 2, 24 or 25 wherein the neuronal therapeutic encoding agent is capable of maintaining axonal generation or regeneration.

34. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is an implant for a neuronal injury site.

35. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is formed upon administration.

36. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is administered to a neuronal injury site.

37. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is a composition selected from the group consisting of a solution, a paste, a suspension, a powder, a semisolid, an emulsion and a gel.

38. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is a paste.

39. The device of any one of claims 1, 2, 24 or 25 wherein the neuronal therapeutic encoding agent is selected from the group consisting of a nucleic acid molecule, a vector, an antisense nucleic acid molecule and a ribozyme.

40. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is complexed with the neuronal therapeutic encoding agent and is capable of binding a neuronal cell surface receptor.

41. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is **conjugated** to the neuronal therapeutic encoding agent and is capable of binding a neuronal cell surface receptor.

42. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is complexed with the neuronal therapeutic encoding agent and is capable of binding a repair cell surface receptor.

43. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is **conjugated** to the neuronal therapeutic encoding agent and is capable of binding a repair cell surface receptor.

44. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is complexed with the neuronal therapeutic encoding agent and is capable of binding extracellular matrix.

45. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is **conjugated** to the neuronal therapeutic encoding agent and is capable of binding extracellular matrix.

46. The device of any one of claims 1, 2, 24 or 25, further comprising a nucleic acid binding domain, wherein said nucleic acid binding domain binds to a nucleic acid sequence that forms a portion of the neuronal therapeutic encoding agent.

47. The device of any one of claims 1, 2, 24 or 25, further comprising at least one linker that is selected from the group consisting of a cleavable linker, a linker that provides an intracellular protein sorting peptide sequence, a linker that reduces steric hindrance, a linker that provides a nuclear translocation signal and a linker that possesses a nucleic acid condensing ability.

48. The device of any one of claims 1, 2, 24 or 25 wherein the device contains sub-physiologic amounts of a neuronal therapeutic agent.

49. The device of any one of claims 1, 2, 24 or 25 wherein the device contains physiologic amounts of a neuronal therapeutic agent.

50. A device according to any one of claims 1, 2, 24 or 25, further comprising a conduit having a lumen.

51. The device of claim 50 wherein the conduit comprises the gene activated matrix.

52. The device of claim 50 wherein the lumen contains the gene activated matrix.

53. The device of claim 50 wherein the conduit comprises a bioabsorbable material.

54. The device of claim 53 wherein the bioabsorbable material comprises material selected from the group consisting of gene activated matrix, type I collagen, laminin, polyglycolic acid, glycolide trimethylene carbonate (GTMC), poly (L-lactide-co-6-caprolactone), glycoproteins, proteoglycans, heparan sulfate proteoglycan, nidogen, glycosaminoglycans, fibronectin, epidermal growth factor, fibroblast growth factor, nerve growth factor, cytokines, and DNA encoding growth factors and cytokines.

55. The device of claim 50 wherein the conduit comprises a non-bioabsorbable material.

56. The device of claim 55 wherein the non-bioabsorbable material is selected from the group consisting of polyamide, polyimide, polyurethane, segmented polyurethane, polycarbonate, and silicone.

57. The device of claim 55 wherein the non-bioabsorbable material comprises an etched microporous synthetic polymer surface.

58. The device of claim 50 wherein the conduit is tubular.

59. A method for transferring a neuronal therapeutic encoding agent into a neuronal cell, comprising: contacting a neuronal cell with the device of any one of claims 1-58 to effectively transfer the neuronal therapeutic encoding agent into the neuronal cell.

60. The method of claim 59 wherein transfer of the neuronal therapeutic encoding agent comprises retrograde axonal transport of the neuronal therapeutic encoding agent.

61. The method of claim 59, further comprising expression of the neuronal therapeutic encoding agent at a neuronal cellular site distinct from a site of contact between the device and the neuronal cell.

62. The method of claim 59 wherein the device is contacted with a neuronal cell at a neuronal injury site.

63. The method of claim 59 wherein the device is contacted with a neuronal cell in a manner such that axonal generation or regeneration occurs.

64. The method of claim 63 wherein axonal regeneration occurs without axonal entrapment.

65. The method of claim 59 wherein the device is contacted with a neuronal cell in a manner that promotes neuronal survival.

66. The method of claim 65 wherein neuronal survival is promoted without axonal entrapment.

67. The method of any one of claims 62, 63, 64, 65 or 66 wherein a neural connection is established or reestablished.

68. A method for transferring a neuronal therapeutic encoding agent into a repair cell, comprising: contacting a repair cell with the device of any one of claims 1-58 to effectively transfer the neuronal therapeutic encoding agent into the repair cell.

69. The method of claim 68 wherein the device is contacted with a repair cell at a neuronal injury site.

70. The method of claim 68 wherein the device is contacted with a repair cell in a manner such that axonal generation or regeneration occurs.

71. The method of claim 70 wherein axonal generation or regeneration occurs without axonal entrapment.

72. The method of claim 68 wherein the device is contacted with a repair cell in a manner that promotes neuronal survival.

73. The method of claim 72 wherein neuronal survival is promoted without axonal entrapment.

74. The method of any one of claims 69, 70, 71, 72 or 73 wherein a neural connection is established or reestablished.

75. The method of either claim 59 or claim 68 wherein the device contains sub-physiologic amounts of a neuronal therapeutic agent.

76. The method of either claim 59 or claim 68 wherein the device contains physiologic amounts of a neuronal therapeutic agent.

77. A method of preparing a gene activated matrix for promoting neuronal regeneration and survival, comprising contacting a neuronal therapeutic encoding agent with a biocompatible matrix such that the neuronal therapeutic encoding agent associates non-covalently with the matrix.

78. The method of claim 77 wherein the neuronal therapeutic encoding agent is adsorbed to the gene activated matrix.

79. The method of claim 77 wherein the neuronal therapeutic encoding agent is absorbed in the gene activated matrix.

80. The method of claim 77 wherein the neuronal therapeutic encoding agent is selected from the group consisting of a nucleic acid molecule, a vector, an antisense molecule and a ribozyme.

L26 ANSWER 4 OF 25 USPATFULL on STN
2004:38576 Methods of diagnosis of breast cancer, compositions and methods of screening for modulators of breast cancer.
Mack, David H., Menlo Park, CA, UNITED STATES
Gish, Kurt C., San Francisco, CA, UNITED STATES
Afar, Daniel, Brisbane, CA, UNITED STATES
Eos Technology, Inc., South San Francisco, CA, UNITED STATES, 94080-7019 (U.S. corporation)
US 2004029114 A1 20040212
APPLICATION: US 2002-58270 A1 20020124 (10)
PRIORITY: US 2001-263965P 20010124 (60)
US 2001-265928P 20010202 (60)
US 2001-282698P 20010409 (60)
US 2001-288590P 20010504 (60)

US 2001-294443P 20010529 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of detecting a breast cancer-associated transcript in a cell from a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-25.

2. The method of claim 1, wherein the biological sample comprises isolated nucleic acids.

3. The method of claim 2, wherein the nucleic acids are mRNA.

4. The method of claim 2, further comprising the step of amplifying nucleic acids before the step of contacting the biological sample with the polynucleotide.

5. The method of claim 1, wherein the polynucleotide comprises a sequence as shown in Tables 1-25.

6. The method of claim 1, wherein the polynucleotide is immobilized on a solid surface.

7. The method of claim 1, wherein the patient is undergoing a therapeutic regimen to treat breast cancer.

8. The method of claim 1, wherein the patient is suspected of having breast cancer.

9. An isolated nucleic acid molecule consisting of a polynucleotide sequence as shown in Tables 1-25.

10. The nucleic acid molecule of claim 9, which is labeled.

11. An expression vector comprising the nucleic acid of claim 9.

12. A host cell comprising the expression vector of claim 11.

13. An isolated polypeptide which is encoded by a nucleic acid molecule having polynucleotide sequence as shown in Tables 1-25.

14. An antibody that specifically binds a polypeptide of claim 13.

15. The antibody of claim 14, further **conjugated** to an effector component.

16. The antibody of claim 15, wherein the effector component is a fluorescent label.

17. The antibody of claim 15, wherein the effector component is a radioisotope or a cytotoxic chemical.

18. The antibody of claim 15, which is an antibody fragment.

19. The antibody of claim 15, which is a humanized antibody

20. A method of detecting a breast cancer cell in a biological sample fromi a patient, the method comprising contacting the biological sample with an antibody of claim 14.

21. The method of claim 20, wherein the antibody is further **conjugated**

to an effector component.

22. The method of claim 21, wherein the effector component is a fluorescent label.

23. A method for identifying a compound that modulates a breast cancer-associated polypeptide, the method comprising the steps of: (i) contacting the compound with a breast cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-25; and (ii) determining the functional effect of the compound upon the polypeptide.

24. A drug screening assay comprising the steps of (i) administering a test compound to a mammal having breast cancer or a cell isolated therefrom; (ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-25 in a treated cell or mammal with the level of gene expression of the polynucleotide in a control cell or mammal, wherein a test compound that modulates the level of expression of the polynucleotide is a candidate for the treatment of breast cancer.

L26 ANSWER 5 OF 25 USPATFULL on STN
2004:7329 Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer.
Mack, David H., Menlo Park, CA, UNITED STATES
Gish, Kurt C., San Francisco, CA, UNITED STATES
Eos Biotechnology, Inc., South San Francisco, CA (U.S. corporation)
US 2004005563 A1 20040108
APPLICATION: US 2002-173999 A1 20020617 (10)
PRIORITY: US 2002-372246P 20020412 (60)
US 2001-350666P 20011113 (60)
US 2001-315287P 20010827 (60)
US 2001-299234P 20010618 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of detecting an ovarian cancer-associated transcript in a cell from a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-20.

2. The method of claim 1, wherein the biological sample comprises isolated nucleic acids.

3. The method of claim 2, wherein the nucleic acids are mRNA.

4. The method of claim 2, further comprising the step of amplifying nucleic acids before the step of contacting the biological sample with the polynucleotide.

5. The method of claim 1, wherein the polynucleotide comprises a sequence as shown in Tables 1-20.

6. The method of claim 1, wherein the polynucleotide is immobilized on a solid surface.

7. The method of claim 1, wherein the patient is undergoing a therapeutic regimen to treat ovarian cancer.

8. The method of claim 1, wherein the patient is suspected of having ovarian cancer.

9. An isolated nucleic acid molecule consisting of a polynucleotide sequence as shown in Tables 1-20.

10. The nucleic acid molecule of claim 9, which is labeled.

11. An expression vector comprising the nucleic acid of claim 9.

12. A host cell comprising the expression vector of claim 11.

13. An isolated polypeptide which is encoded by a nucleic acid molecule having polynucleotide sequence as shown in Tables 1-20.

14. An antibody that specifically binds a polypeptide of claim 13.

15. The antibody of claim 14, further **conjugated** to an effector component.

16. The antibody of claim 15, wherein the effector component is a fluorescent label.

17. The antibody of claim 15, wherein the effector component is a radioisotope or a cytotoxic chemical.

18. The antibody of claim 15, which is an antibody fragment.

19. The antibody of claim 15, which is a humanized antibody

20. A method of detecting an ovarian cancer cell in a biological sample from a patient, the method comprising contacting the biological sample with an antibody of claim 14.

21. The method of claim 20, wherein the antibody is further **conjugated** to an effector component.

22. The method of claim 21, wherein the effector component is a fluorescent label.

23. A method for identifying a compound that modulates an ovarian cancer-associated polypeptide, the method comprising the steps of: (i) contacting the compound with an ovarian cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-20; and (ii) determining the functional effect of the compound upon the polypeptide.

24. A drug screening assay comprising the steps of (i) administering a test compound to a mammal having ovarian cancer or a cell isolated therefrom; (ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-20 in a treated cell or mammal with the level of gene expression of the polynucleotide in a control cell or mammal, wherein a test compound that modulates the level of expression of the polynucleotide is a candidate for the treatment of ovarian cancer.

L26 ANSWER 6 OF 25 USPATFULL on STN
2003:314633 Hybrid polypeptides with enhanced pharmacokinetic properties.

Barney, Shawn, Apex, NC, United States
Guthrie, Kelly I., Virginia Beach, VA, United States
Merutka, Gene, Saratoga, CA, United States
Anwer, Mohmed K., Foster City, CA, United States
Lambert, Dennis M., Cary, NC, United States
Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6656906 B1 20031202
APPLICATION: US 1999-350641 19990709 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A hybrid polypeptide comprising a core polypeptide linked to an enhancer peptide, wherein the core polypeptide comprises the following amino acid sequence: YTSLIHSLIEESQNQQEKNEQELLELDK; LEENITALLEEAQIQQEKNMYELQKLNS; LEANISQSLEQAQIQQEKNMYELQKLNS; NNYTSLIHSLIEESQNQQEKNEQELLEL; DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL; RYLEANITALLEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK; TALLEQAQIQQEKNEYELQKLDE; TALLEQAQIQQEKNEYELQKLIE; TALLEQAQIQQEKIEYELQKLDK; TALLEQAQIQQEKIEYELQKLDE; TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE; TALLEQAQIQQEKIEYELQKLAK; TALLEQAQIQQEKIEYELQKLAE; TALLEQAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE; TALLEQAQIQQEKGEYELQKLE; TALLEQAQIQQEKAEYELQKLAK; TALLEQAQIQQEKNEYELQKLAK; TALLEQAQIQQEKGEYELQKLAK; TALLEQAQIQQEKAEYELQKLAE; TALLEQAQIQQEKNEYELQKLAE; TALLEQAQIQQEKGEYELQKLAE; DEFDASISQVNEKINQSLAFIRKSDELL; DEYDASISQVNEKINQALAYIREADEL; DEYDASISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL; DEFDESISQVNEKIEESLAFIRKSDEL; or QHWSYGLRPG (SEQ ID NOS:1278-1285 and 1287-1309, respectively); wherein the enhancer peptide sequence comprises WQEWEQKI (SEQ ID NO:1129) or WASLWEWF (SEQ ID NO:1433).

2. The hybrid polypeptide of claim 1, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide.

3. The hybrid polypeptide of claim 2, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

4. The hybrid polypeptide of claim 1, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.

5. A polypeptide comprising the amino acid sequence: VYPSDEYDASISQVNEEINQALAYIRKADELLENV (SEQ ID NO:692).

6. The polypeptide of claim 5, further comprising an amino-terminal acetyl group and a carboxy-terminal amido group.

7. A core polypeptide comprising:

RYLEANISQSLEQAQIQQEKNMYELQKL (SEQ ID NO:1283);
RYLEANITALLEQAQIQQEKNEYELQKL (SEQ ID NO:1284);
TALLEQAQIQQEKNEYELQKLDE (SEQ ID NO:1287);
TALLEQAQIQQEKNEYELQKLIE (SEQ ID NO:1288);
TALLEQAQIQQEKIEYELQKLDK (SEQ ID NO:1289);
TALLEQAQIQQEKIEYELQKLDE (SEQ ID NO:1290);
TALLEQAQIQQEKIEYELQKLIE (SEQ ID NO:1291);
TALLEQAQIQQEKIEYELQKLE (SEQ ID NO:1292);
TALLEQAQIQQEKIEYELQKLAK (SEQ ID NO:1293);
TALLEQAQIQQEKIEYELQKLAE (SEQ ID NO:1294);
TALLEQAQIQQEKAEYELQKLE (SEQ ID NO:1295);
TALLEQAQIQQEKNEYELQKLE (SEQ ID NO:1296);
TALLEQAQIQQEKGEYELQKLE (SEQ ID NO:1297);

TALLEQAQIQQEKAEYELQKLAK (SEQ ID NO:1298);
TALLEQAQIQQEKNEYELQKLAK (SEQ ID NO:1299);
TALLEQAQIQQEKGEYELQKLAK (SEQ ID NO:1300);
TALLEQAQIQQEKAEYELQKLAE (SEQ ID NO:1301);
TALLEQAQIQQEKNEYELQKLAE (SEQ ID NO:1302);
TALLEQAQIQQEKGEYELQKLAE (SEQ ID NO:1303);
DEYDASISQVNEKINQALAYIREADEL (SEQ ID NO:1304);
DEYDASISQVNEEINQALAYIRKADEL (SEQ ID NO:1306);
DEFDESISQVNEKIEESLAFIRKSDELL (SEQ ID NO:1307); or
DEFDESISQVNEKIEESLAFIRKSDEL (SEQ ID NO:1308).

8. A method for enhancing the pharmacokinetic properties of a core polypeptide comprising linking an enhancer peptide sequence to a core polypeptide, wherein the enhancer peptide comprises an amino-terminal or carboxy-terminal sequence WXXWXXXI or IXXXWXXW, to form a hybrid polypeptide, such that, when introduced into a living system, the hybrid polypeptide exhibits enhanced pharmacokinetic properties relative to those exhibited by the core polypeptide.

9. A method for enhancing the pharmacokinetic properties of a core polypeptide comprising linking an enhancer peptide to a heteropolymeric core polypeptide, wherein the enhancer peptide comprises an amino-terminal or carboxy-terminal sequence WXXWXXXI, IXXXWXXW, WXXWXXX, WXXXWXwx, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, XXXWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW, and wherein the heteropolymeric core polypeptide comprises at least about 94 amino acid residues, to form a hybrid polypeptide such that, when introduced into a living system, the hybrid polypeptide exhibits enhanced pharmacokinetic properties relative to those exhibited by the heteropolymeric core polypeptide.

10. A hybrid polypeptide comprising an enhancer peptide linked to a core polypeptide, wherein the enhancer peptide comprises an amino-terminal or carboxy-terminal sequence WXXWXXXI or IXXXWXXW.

11. A hybrid polypeptide comprising an enhancer peptide linked to a heteropolymeric core polypeptide, wherein the enhancer peptide comprises an amino-terminal or carboxy-terminal sequence WXXWXXXI, IXXXWXXW, WXXWXXX, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, XXXWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW, and wherein the heteropolymeric core polypeptide comprises at least about 94 amino acid residues.

12. A hybrid polypeptide comprising an enhancer peptide linked to a core polypeptide, wherein the core polypeptide sequence comprises the following amino acid sequence: RYLEANISQSLEQAQIQQEKNMYELQKL; RYLEANITALLEQAQIQQEKNEYELQKL; TALLEQAQIQQEKNEYELQKLDE; TALLEQAQIQQEKNEYELQKLIE; TALLEQAQIQQEKIEYELQKLDK; TALLEQAQIQQEKIEYELQKLDE; TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE; TALLEQAQIQQEKIEYELQKLAK; TALLEQAQIQQEKIEYELQKLAE; TALLEQAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE; TALLEQAQIQQEKGEYELQKLE; TALLEQAQIQQEKAEYELQKLAK; TALLEQAQIQQEKNEYELQKLAK; TALLEQAQIQQEKGEYELQKLAK; TALLEQAQIQQEKAEYELQKLAE; TALLEQAQIQQEKNEYELQKLAE; TALLEQAQIQQEKGEYELQKLAE; DEYDASISQVNEKINQALAYIREADEL; DEYDASISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL; or DEFDESISQVNEKIEESLAFIRKSDEL (SEQ ID NOS:1283-1284, 1287-1303, 1305-1308, respectively).

13. The hybrid polypeptide of claim 12, wherein the enhancer peptide is linked to the amino-terminal end of the core polypeptide.

14. The hybrid polypeptide of claim 13, further comprising an enhancer

peptide linked to the carboxy-tenninal end of the core polypeptide.

15. The hybrid polypeptide of claim 12, wherein the enhancer peptide is linked to the carboxy-terminal end of the core polypeptide.

16. A hybrid polypeptide comprising an enhancer peptide linked to the carboxy terminus of a core polypeptide, wherein the core polypeptide comprises the sequence YTSLIHSLIEESQNQQEKNEQELLELDK (SEQ ID NO:1278), and wherein the enhancer peptide comprises a carboxy-terminal sequence WXXWXXXI, IXXXWXXW, WXXWXXX, WXXWXX, WXXWX, WXXW, XXXWXWX, XXWXWX, XWXWX, WXWX, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW.

17. A hybrid polypeptide comprising an enhancer peptide linked to a core polypeptide, wherein the core polypeptide comprises the sequence NNYTSLIHSLIEESQNQQEKNEQELLEL (SEQ ID NO:1281); DEFDASISQVNEKINQSLAFIRKSDELL (SEQ ID NO:1304); or QHWSYGLRPG (SEQ ID NO:1309); and wherein the enhancer peptide is 4 to about 30 amino acids in length, and comprises an amino-terminal or carboxy-terminal sequence WXXWXXXI, IXXXWXXW, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW.

18. A method for enhancing the pharmacokinetic properties of a core polypeptide, comprising linking an enhancer peptide sequence to the core polypeptide to produce a hybrid polypeptide, wherein the enhancer peptide sequence comprises WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW; wherein the core polypeptide comprises TALLEQAQIQQEKNEYELQKLDK (SEQ ID NO:1286), and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated** such that, when introduced into a living system, the hybrid polypeptide exhibits enhanced pharmacokinetic properties relative to those exhibited by the core polypeptide.

19. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence comprises an amino-terminal WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW; wherein the core polypeptide comprises TALLEQAQIQQEKNEYELQKLDK (SEQ ID NO:1286), and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

20. The hybrid polypeptide of claim 19, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

21. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence comprises WQEWEQKI (SEQ ID NO:1129) or WASLWEWF (SEQ ID NO:1433); wherein the core polypeptide comprises TALLEQAQIQQEKNEYELQKLDK (SEQ ID NO:1286), and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

22. A polypeptide comprising the amino acid sequence WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO:1310), wherein at least one amino acid residue of the polypeptide is polyol-**conjugated**.

23. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence comprises a

carboxy-terminal WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW; wherein the core polypeptide comprises TALLEQAQIQQEKNEYELQKLDK (SEQ ID NO:1286), and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

24. The hybrid polypeptide of claim 23, further comprising an enhancer peptide sequence linked to the amino-terminal end of the core polypeptide.

25. A polypeptide comprising TALLEQAQIQQEKNEYELQKLDK (SEQ ID NO:1286), wherein at least one amino acid residue of the polypeptide is polyol-**conjugated**.

26. A pharmaceutical composition comprising the polypeptide TALLEQAQIQQEKNEYELQKLDK (SEQ ID NO:1286), wherein at least one amino acid residue of the polypeptide is polyol-**conjugated**, and a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising the polypeptide WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF (SEQ ID NO:1310), wherein at least one amino acid residue of the polypeptide is polyol-**conjugated**, and a pharmaceutically acceptable carrier.

28. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence comprises WQEWEQKI (SEQ ID NO:1129) or WASLWEWF (SEQ ID NO:1433); and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

29. The hybrid polypeptide of claim 28, wherein the enhancer peptide sequence is linked to the amino terminus of the core polypeptide.

30. The hybrid polypeptide of claim 29, further comprising an enhancer peptide sequence linked to the carboxy terminus of the core polypeptide.

31. The hybrid polypeptide of claim 28, wherein the enhancer peptide sequence is linked to the carboxy terminus of the core polypeptide.

32. The hybrid polypeptide of claim 28, wherein the enhancer peptide sequence comprises WQEWEQKI (SEQ ID NO:1129).

33. The hybrid polypeptide of claim 28, wherein the enhancer peptide sequence comprises WASLWEWF (SEQ ID NO:1433).

34. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence comprises an amino-terminal WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW; wherein the core polypeptide comprises the following amino acid sequence: LEENITALLEEAQIQQEKNMYELQKLNS; LEANISQSLEQAQIQQEKNMYELQKLNS; DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL; RYLEANITALLEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK; TALLEQAQIQQEKNEYELQKLDE; TALLEQAQIQQEKNEYELQKLIE; TALLEQAQIQQEKIEYELQKLDK; TALLEQAQIQQEKIEYELQKLDE; TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE; TALLEQAQIQQEKIEYELQKLAK, TALLEQAQIQQEKIEYELQKLAE; TALLEQAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE; TALLEQAQIQQEKGEYELQKLE; TALLEQAQIQQEKAEYELQKLAK; TALLEQAQIQQEKNEYELQKLAK; TALLEQAQIQQEKGEYELQKLAK; TALLEQAQIQQEKAEYELQKLAE; TALLEQAQIQQEKNEYELQKLAE;

TALLEQAQIQQEKGEYELQKLAE; DEFDASISQVNEKINQSKAFIRKSDELL;
DEYDASISQVNEKINQALAYIREADEL; DEYDASISQVNEEINQALAYIRKADEL;
DEFDESISQVNEKIEESLAFIRKSDELL; DEFDESISQVNEKIESSKLAFIRKSDEL; or
QHWYSYGLRPG (SEQ ID NOS:1279, 1280, 1282-1285, and 1287-1309,
respectively); and wherein at least one amino acid residue of the hybrid
polypeptide is polyol-**conjugated**.

35. The hybrid polypeptide of claim 34, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

36. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence comprises WQEWEQKI (SEQ ID NO:1129) or WASLWEWF (SEQ ID NO:1433); wherein the core polypeptide comprises the following amino acid sequence
YTSLIHSLIEESQNQQEKNEQELLELDK; LEENITALLEEAQIQQEKNMYELQKLNS;
LEANISQSLEQAQIQQEKNMYELQKLNS; NYTSLIHSLIEESQNQQEKNEQELLEL;
DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL;
RYLEANITALLEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK;
TALLEQAQIQQEKNEYELQKLDE; TALLEQAQIQQEKNEYELQKLIE;
TALLEQAQIQQEKIEYELQKLDK; TALLEQAQIQQEKIEYELQKLDE;
TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE; TALLEQAQIQQEKIEYELQKLAK;
TALLEQAQIQQEKIEYELQKLAE; TALLEQAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE;
TALLEQAQIQQEKGEYELQKLE; TALLEQAQIQQEKAEYELQKLAK;
TALLEQAQIQQEKNEYELQKLAK; TALLEQAQIQQEKGEYELQKLAK;
TALLEQAQIQQEKAEYELQKLAE; TALLEQAQIQQEKNEYELQKLAE;
TALLEQAQIQQEKGEYELQKLAE; DEFDASISQVNEKINQSLAFIRKSDELL;
DEYDASISQVNEKINQALAYIREADEL; DEYDASISQVNEEINQALAYIRKADEL;
DEFDESISQVNEKIEESLAFIRDSDELL; DEFDESISQVNEKIEESLAFIRDSDEL; or QHWSYGLRPG
(SEQ ID NOS:1278-1285 and 1287-1309, respectively); and wherein at least
one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

37. The hybrid polypeptide of claim 36, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide.

38. The hybrid polypeptide of claim 37, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

39. The hybrid polypeptide of claim 36, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.

40. The hybrid polypeptide of claim 36, wherein the hybrid polypeptide comprises the amino acid sequence WQEWEQKITALLEQAQIQQEKIEYELQKLIEWEWF (SEQ ID NO:1311).

41. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence comprises a carboxy-terminal WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX,
XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, IXXXWXXW, XXXWXXW,
XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW;
wherein the core polypeptide comprises the following amino acid sequence
LEENITALLEEAQIQQEKNMYELQKLNS; LEANISQSLEQAQIQQEKNMYELQKLNS:
DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL;
RYLEANITALLEQAQIQQEKNEYELQKL; TALLEQAQIQQEKNEYELQKLDE;
TALLEQAQIQQEKNEYELQKLIE; TALLEQAQIQQEKIEYELQKLDK;
TALLEQAQIQQEKIEYELQKLDE; TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE;
TALLEQAQIQQEKIEYELQKLAK; TALLEQAQIQQEKIEYELQKLAE;
TALLEQAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE; TALLEQAQIQQEKGEYELQKLE;
TALLEQAQIQQEKAEYELQKLAK; TALLEQAQIQQEKNEYELQKLAK;
TALLEQAQIQQEKGEYELQKLAK; TALLEQAQIQQEKAEYELQKLAE;
TALLEQAQIQQEKNEYELQKLAE; TALLEQAQIQQEKGEYELQKLAE;

DEFDASISQVNEKINQSLAFIRKSDELL; DEYDADISQVNEKINQALAYIREADEL; DEYDASISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL; DEFDESISQVNEKIEESLAFIRKSDEL; or QHWSYGLRPG (SEQ ID NOS:1279, 1280, 1282-1284, and 1287-1309, respectively); and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

42. The hybrid polypeptide of claim 41, further comprising an enhancer peptide sequence linked to the amino-terminal end of the core polypeptide.

43. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide and comprises an amino-terminal WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW; wherein the core polypeptide comprises NNYTSLIHSLIEESQNQQEKNEQELLEL (SEQ ID NO:1281), and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

44. The hybrid polypeptide of claim 43, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

45. A hybrid polypeptide comprising an enhancer-peptide sequence linked to a core polypeptide, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide and comprises a carboxy-terminal WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW; wherein the core polypeptide comprises NNYTSLIHSLIEESQNQQEKNEQELLEL (SEQ ID NO:1281), and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

46. The hybrid polypeptide of claim 45, further comprising an enhancer peptide sequence linked to the amino-terminal end of the core polypeptide.

47. A hybrid polypeptide comprising an enhancer peptide sequence linked to the amino-terminal end of a core polypeptide, wherein the enhancer peptide sequence comprises an amino-terminal WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXWX, WXXXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW; wherein the core polypeptide comprises YTSLIHSLIEESQNQQEKNEQELLELDK (SEQ ID NO:1278), and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

48. The hybrid polypeptide of claim 47, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

49. A hybrid polypeptide comprising a core polypeptide linked to an enhancer peptide sequence, wherein the core polypeptide comprises the following amino acid sequence YTSLIHSLIEESQNQQEKNEQELLELDK; LEENITALLEEAQIQQEKNMYELQKLNS; LEANISQSLEQAQIQQEKNMYELQKLNS; NNYTSLIHSLIEESQNQQEKNEQELLEL; DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL; RYLEANITALLEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK; TALLEQAQIQQEKNEYELQKLDE; TALLEQAQIQQEKNEYELQKLIE; TALLEQAQIQQEKIEYELQKLDK; TALLEQAQIQQEKIEYELQKLDE; TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE; TALLEQAQIQQEKIEYELQKLAK; TALLEQAQIQQEKIEYELQKLAE; TALLEQAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE; TALLEQAQIQQEKGEYELQKLE;

TALLEQAQIQQEKAEYELQKLAK; TALLEQAQIQQEKNEYELQKLAK;
TALLEQAQIQQEKGEYELQKLAK; TALLEQAQIQQEKAEYELQKLAE;
TALLEQAQIQQEKNEYELQKLAE; TALLEQAQIQQEKGEYELQKLAE;
DEFDASISQVNEKINQSLAFIRKSDELL; DEYDASISQVNEKINQALAYIREADEL;
DEYDASISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL;
DEFDESISQVNEKIEESLAFIRKSDEL; or QHWSYGLRPG (SEQ ID NOS:1278-1285 and 1287-1309, respectively); wherein the enhancer peptide sequence comprises WQEWEQKI (SEQ ID NO:1129) or WASLWEWF (SEQ ID NO:1433); and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

50. The hybrid polypeptide of claim 49, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide.

51. The hybrid polypeptide of claim 50, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

52. The hybrid polypeptide of claim 49, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.

53. A polypeptide comprising the amino acid sequence VYPSDEYDASISQVNEEINQALAYIRKADELLENV (SEQ ID NO:692), wherein at least one amino acid residue of the polypeptide is polyol-**conjugated**.

54. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide, wherein the core polypeptide comprises the amino acid sequence RYLEANISQSLEQAQIQQEKNMYELQKL; RYLEANITALLEQAQIQQEKNEYELQKL; TALLEQAQIQQEKNEYELQKLDE; TALLEQAQIQQEKNEYELQKLIE; TALLEQAQIQQEKIEYELQKLDK; TALLEQAQIQQEKIEYELQKLDE; TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE; TALLEQAQIQQEKIEYELQKLAK; TALLEQAQIQQEKIEYELQKLAE; TALLEQAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE; TALLEQAQIQQEKGEYELQKLE; TALLEQAQIQQEKAEYELQKLAK; TALLEQAQIQQEKNEYELQKLAK; TALLEQAQIQQEKGEYELQKLAK; TALLEQAQIQQEKAEYELQKLAE; TALLEQAQIQQEKNEYELQKLAE; TALLEQAQIQQEKGEYELQKLAE; DEYDADISQVNEKINQALAYIREADEL; DEYDASISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL; or DEFDESISQVNEKIEESLAFIRKSDEL (SEQ ID NOS:1283, 1284, 1287-1303, 1305-1308, respectively); and wherein at least one amino acid residue of the hybrid polypeptide is polyol-**conjugated**.

55. The hybrid polypeptide of claim 54, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide.

56. The hybrid polypeptide of claim 55, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

57. The hybrid polypeptide of claim 54, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.

58. The hybrid polypeptide of any of claims 19-21, 23-24, 28-52 and 54-57, wherein the enhancer polypeptide sequence comprises WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, XXXWXWX, XXWXWX, XWXWX, WXWX, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW or XWXXXW, further comprising an amino-terminal acetyl group and a carboxy-terminal amido group.

59. The polypeptide of claims 22, 25, or 53, further comprising an amino-terminal acetyl group and a carboxy-terminal amido group.

60. The hybrid polypeptide of any of claims 19-21, 23-24, 28-52 and

54-57, wherein the core polypeptide is a therapeutic reagent, further wherein the enhancer polypeptide sequence comprises WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, XXXWXWX, XXWXWX, XWXWX, WXWX, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW or XWXXXW.

61. The hybrid polypeptide of any of claims 19-21, 23-24, 28-52 and 54-57, wherein the enhancer polypeptide sequence comprises WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, XXXWXWX, XXWXWX, XWXWX, WXWX, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW or XWXXXW, further wherein the polyol is poly(propylene glycol), polyethylene-polypropylene glycol or poly(ethylene glycol).

62. The hybrid polypeptide of claim 61, wherein the polyol is a straight-chain polyol.

63. The hybrid polypeptide of claim 61, wherein the polyol is a branched-chain polyol.

64. The polypeptide of any of claims 22, 25, and 53, wherein the polyol is poly(propylene glycol), polyethylene-polypropylene glycol or poly(ethylene glycol).

65. The polypeptide of claim 64, wherein the polyol is a straight-chain polyol.

66. The polypeptide of claim 64, wherein the polyol is a branched-chain polyol.

67. The pharmaceutical composition of claim 26 or 27, wherein the polypeptide further comprises an amino-terminal acetyl group and a carboxy-terminal amido group.

68. The pharmaceutical composition of claim 26 or 27, wherein the polyol, used to **conjugate** the polypeptide, is poly(propylene glycol), polyethylene-polypropylene glycol or poly(ethylene glycol).

69. A hybrid polypeptide comprising an enhancer peptide linked to the carboxy terminus of a core polypeptide, wherein the core polypeptide comprises the sequence NNYTSLIHSLIEESQNQQEKNEQELLELDK (SEQ ID NO:1285); and wherein the enhancer peptide comprises the sequence WXXWXXXI, IXXXWXXW, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW.

70. A hybrid polypeptide comprising an enhancer peptide linked to a core polypeptide, wherein the core polypeptide comprises the sequence NNYTSLIHSLIEESQNQQEKNEQELLELDK (SEQ ID NO:1285); and wherein the enhancer peptide is 4 to about 30 amino acids in length, and comprises an amino-terminal or carboxy-terminal sequence WXXWXXXI, IXXXWXXW, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, XXXWXXW, XXWXXW, XWXXW, XWXWXXXW, XWXWXXX, XWXWXX, XWXW, WXWXXXW, or XWXXXW.

71. The hybrid polypeptide of claim 69 or 70, further comprising an amino-terminal acetyl group and a carboxy-terminal amido group.

72. The hybrid polypeptide of claim 69, wherein at least one amino acid residue of the hybrid polypepide is polyol-**conjugated**.

73. The hybrid polypeptide of claim 72, wherein the polyol is a straight-chain polyol.

74. The hybrid polypeptide of claim 72, wherein the polyol is a branched-chain polyol.

75. The hybrid polypeptide of claim 70, wherein at least one amino acid residue of the hybrid polypeptide is polyol-conjugated.

76. The hybrid polypeptide of claim 75, wherein the polyol is a straight-chain polyol.

77. The hybrid polypeptide of claim 75, wherein the polyol is a branched-chain polyol.

78. The hybrid polypeptide of claim 71, wherein at least one amino acid residue of the hybrid polypeptide is polyol-conjugated.

79. The hybrid polypeptide of claim 78, wherein the polyol is a straight-chain polyol.

80. The hybrid polypeptide of claim 78, wherein the polyol is a branched-chain polyol.

81. A method for enhancing the pharmacokinetic properties of a core polypeptide comprising linking an enhancer peptide to a heteropolymeric core polypeptide, wherein the enhancer peptide consists of an amino-terminal or carboxy-terminal sequence WXXWXX, WXXWX, WXXW, XXWXXW, or XWXXW; and wherein the heteropolymeric core polypeptide comprises at least about 94 amino acid residues, to form a hybrid polypeptide such that, when introduced into a living system, the hybrid polypeptide exhibits enhanced pharmacokinetic properties relative to those exhibited by the heteropolymeric core polypeptide.

82. A hybrid polypeptide comprising an enhancer peptide linked to a heteropolymeric core polypeptide, wherein the enhancer peptide consists of an amino-terminal or carboxy-terminal sequence WXXWXX or XXWXXW; and wherein the heteropolymeric core polypeptide comprises at least about 94 amino acid residues.

L26 ANSWER 7 OF 25 USPATFULL on STN
2003:264865 Therapy for human cancers using cisplatin and other drugs or genes encapsulated into liposomes.
Boulikas, Teni, Palo Alto, CA, UNITED STATES
US 2003185879 A1 20031002
APPLICATION: US 2003-350470 A1 20030123 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for producing cisplatin micelles, comprising: a) combining cisplatin and a phosphatidyl glycerol lipid derivative in a range of 1:1 to 1:2 to form a cisplatin mixture; and b) combining the mixture of step a) with an effective amount of at least a 30% ethanol solution to form cisplatin micelles.

2. A method for producing cisplatin micelles, comprising: a) combining cisplatin with an effective amount of at least a 30% ethanol solution to form a cisplatin/ethanol solution; and b) combining the solution with a phosphatidyl glycerol lipid derivative in a range of 1:1 to 1:2 to form cisplatin micelles.

3. The method of claim 1 or 2, wherein the phosphatidyl glycerol lipid derivative is selected from the group consisting of dipalmitoyl phosphatidyl glycerol (DPPG), dimyristoyl phosphatidyl glycerol (DMPG),

dicaproyl phosphatidyl glycerol (DCPG), distearoyl phosphatidyl glycerol (DSPG) and dioleyl phosphatidyl glycerol (DOPG).

4. The method of claim 1 or 2, wherein the molar ratio is 1:1.

5. The method of claim 1 or 2, further comprising combining an effective amount of a free fusogenic peptide, a fusogenic peptide-lipid conjugate or a fusogenic peptide-PEG-HSPC conjugate to the mixture of step a) where the fusogenic peptide is derivatized with a stretch of 1-6 negatively-charged amino acids at the N or C-terminus and thus, able to bind electrostatically to aquaplatin.

6. The method of claim 5, wherein the free fusogenic peptide or fusogenic peptide lipid conjugate comprises DOPE or DOPE/cationic lipid.

7. The cisplatin micelle obtained by the method of claims 1 or 2.

8. The cisplatin micelle obtained by the method of claim 5.

9. A method for encapsulating cisplatin micelles, comprising mixing an effective amount of a vesicle-forming lipid with the cisplatin micelles of claim 1 or 2.

10. The encapsulated cisplatin obtainable by the method of claim 9.

11. The method of claim 10, wherein the lipid is selected from premade neutral liposomes, composed of cholesterol 10-60%, hydrogenated soy phosphatidylcholine (HSPC) 40-90% and polyethyleucglycol (PEG)-HSPC 1-7% or lipids in solution, lipids in powder and PEG-DSPE.

12. The method of claim 10, wherein the lipid comprises 10-60% cholesterol.

13. A method for obtaining a cisplatin/lipid complex capable of evading macrophages and cells of the immune system when administered to a subject, the method comprising mixing an effective amount of the cisplatin micelles of claim 9 with an effective amount of PEG-DSPE, PEG-DSPC or hyaluronic acid-DSPE.

14. The method of claim 1 or 2, further comprising removal of the ethanol from the cisplatin micelles.

15. The method of claim 14, wherein removal of the ethanol is by dialysis of the micelles through permeable membranes to remove the ethanol.

16. Encapsulated cisplatin obtainable by the method of claim 11.

17. Encapsulated cisplatin obtainable by the method of claim 13.

18. A method for delivering cisplatin to a cell comprising contacting the cell with the encapsulated cisplatin of claim 15.

19. A method for delivering cisplatin to a cell comprising contacting the cell with the encapsulated cisplatin of claim 17.

20. A method for inhibiting the growth of a tumor in a subject, comprising administering to the subject an effective amount of the encapsulated cisplatin of claim 16.

21. A method for inhibiting the growth of a tumor in a subject, comprising administering to the subject an effective amount of the

encapsulated cisplatin of claim 17.

22. A method for targeting solid tumors and metastases in a subject comprising intravenous administration of an effective amount of the encapsulated cisplatin of claims 16 or 17.

23. A method for penetrating the cell membrane of a tumor in a subject comprising administering an effective amount of the cisplatin micelle obtainable by the method of claim 7.

24. A method for inhibiting tumor growth in a subject comprising administering to the subject an effective amount of the encapsulated cisplatin of claim 10 and a gene selected from the group consisting of p53, pax5 and HSV-tk genes.

24a. The method of claim 24, wherein the method further comprises administering an effective amount of encapsulated ganciclovir.

25. The method of claim 24 wherein the genes to be combined with cisplatin are any of, or combinations of encapsulated IL-2, IL-4, IL-7, IL-12, GM-CSF, IFN-gamma, TNF-alpha, RB, BRCA1, E1A, cytosine deaminase in combination with encapsulated 5-fluorcytosine, bcl -2, MDR-1, p21, p16, bax, bcl-xs, E2F, IGFI, VEGF, TGF-beta and the like.

26. A composition comprising the encapsulated cisplatin of claim 10 and encapsulated oligonucleotides, ribozymes, triplex, PNA.

27. A composition comprising the encapsulated cisplatin of claim 10 and a drug selected from the group consisting of doxorubicin, fluorodeoxyuridine, bleomycin, adriamycin, vinblastin, prednisone, vincristine, taxol.

L26 ANSWER 8 OF 25 USPATFULL on STN
2003:206860 Compositions containing nucleic acids and ligands for therapeutic treatment.
Baird, J. Andrew, London, UNITED KINGDOM
Chandler, Lois Ann, Encinitas, CA, UNITED STATES
Sosnowski, Barbara A., Coronado, CA, UNITED STATES
Selective Genetics, Inc., San Diego, CA (non-U.S. corporation)
US 2003143217 A1 20030731
APPLICATION: US 2002-189360 A1 20020702 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A pharmaceutical composition having the formula: receptor-binding internalized ligand-nucleic acid binding domain-cytocide-encoding agent, wherein: receptor-binding internalized ligand is a polypeptide reactive with a cell surface receptor; nucleic acid binding domain binds to a nucleic acid, the domain being chemically **conjugated** or fused to the receptor-binding internalized ligand; cytocide-encoding agent is a nucleic acid molecule encoding a cytocide, the agent being bound to the nucleic acid binding domain; and wherein the receptor-binding internalized ligand-nucleic acid binding domain-cytocide-encoding agent binds to the cell surface receptor and internalizes the cytocide-encoding agent in cells bearing the receptor.

2. A pharmaceutical composition having the formula: receptor-binding internalized ligand-nucleic acid binding domain-prodrug-encoding agent, wherein: receptor-binding internalized ligand is a polypeptide reactive with a cell surface receptor; nucleic acid binding domain binds to a nucleic acid, the domain being chemically **conjugated** or fused to the

receptor-binding internalized ligand; prodrug-encoding agent is a nucleic acid molecule encoding a prodrug, the agent being bound to the nucleic acid binding domain; and wherein the receptor-binding internalized ligand-nucleic acid binding domain-prodrug-encoding agent binds to the cell surface receptor and internalizes the cytocide-encoding agent in cells bearing the receptor.

3. The composition of either of claims 1 or 2 wherein the receptor-binding internalized ligand is a polypeptide reactive with an FGF receptor.

4. The composition of either of claims 1 or 2 wherein the receptor-binding internalized ligand is selected from the group consisting of a polypeptide reactive with a VEGF receptor and a polypeptide reactive with an HBEGF receptor and a cytokine.

5. The composition of claim 1 wherein the cytocide-encoding agent encodes a protein that inhibits protein synthesis.

6. The composition of claim 5 wherein the protein is a ribosome inactivating protein.

7. The composition of claim 6 wherein the ribosome inactivating protein is saporin.

8. The composition of claim 6 wherein the ribosome inactivating protein is gelonin.

9. The composition of claim S wherein the protein inhibits elongation factor 2.

10. The composition of claim 9 wherein the protein is diphtheria toxin.

11. The composition of claim 2 wherein the prodrug-encoding agent encodes HSV-thymidine kinase or cytosine deaminase.

12. The composition of either of claims 1 or 2 wherein the growth factor is a polypeptide reactive with the FGF receptor and the nucleic acid binding domain is poly-L-lysine.

13. The composition of either of claims 1 or 2 wherein the nucleic acid binding domain is selected from the group consisting of helix-turn-helix motif proteins, homeodomain proteins, zinc finger motif proteins, steroid receptor proteins, leucine zipper motif proteins, helix-loop-helix motif proteins, and β-sheet motif proteins.

14. The composition of either of claims 1 or 2 wherein the nucleic acid binding domain is selected from the group consisting of AP-1, Sp-1, rev, GCN4, λcro, λcI, TFIIA, myoD, retinoic acid receptor, glucocosteroid receptor, SV40 large T antigen, and GAL4.

15. The composition of either of claims 1 or 2 wherein the nucleic acid binding domain is a polycation.

16. The composition of claim 15 wherein the polycation is selected from the group consisting of poly-L-lysine, protamine, histone and spermine.

17. The composition of claim 1 wherein the nucleic acid binding domain binds a DNA molecule that encodes a ribosome inactivating protein.

18. The composition of claim 1 wherein the nucleic acid binding domain binds the coding region of saporin DNA.

19. The composition of claim 1 wherein the cytocide-encoding agent further comprises a tissue-specific promoter.

20. The composition of claim 2 wherein the prodrug-encoding agent further comprises a tissue-specific promoter.

21. The composition of either of claims 19 or 20 wherein the tissue-specific promoter is selected from the group consisting of alpha-crystalline, tyrosinase, α-fetoprotein, prostate specific antigen, CEA, α-actin, VEGF receptor, erbB-2, C-myc, cyclin D, FGF receptor and gamma-crystalline promoter.

22. The composition of either of claims 19 or 20 wherein the tissue specific promoter is endothelial cell specific.

23. The composition of claim 22 wherein the endothelial-specific promoter is selected from the group consisting of VEGF receptor, tek, tie, urokinase receptor, E-selectin, P-selectin, VCAM-1, endoglin, endosialin, alphav integrin, β3 integrin, endothelin-1, ICAM-3, E9, von Willebrand Factor, CD-44, CD40, vascular endothelial cadherin, notch 4 and high molecular weight melanoma-associated antigen.

24. The composition of any one of claims 1-23, further comprising at least one linker that increases the serum stability, intracellular availability, or condensing ability of the nucleic acid binding domain, the addition of said linker(s) resulting in the formula: receptor-binding internalized ligand-(L)q-nucleic acid binding domain-cytocide encoding agent or the formula: receptor-binding internalized ligand-(L)q-nucleic acid binding domain-prodrug encoding agent wherein: L is at least one linker; and q is 1 or more, such that the **conjugate** retains the ability to bind to a cell surface receptor and internalize the cytocide-encoding agent, and wherein the cytocide-encoding agent is bound to the nucleic acid binding domain.

25. The composition of claim 24 wherein the linker increases the flexibility of the **conjugate**.

26. The composition of claim 25 wherein the linker is selected from the group consisting of (GlymSerp)n, (SermGlyp)n and (AlaAlaProAla)n in which n is 1 to 6, m is 1 to 6 and p is 1 to 4.

27. The composition of claim 26 wherein m is 4, p is 1 and n is 2 to 4.

28. The composition of claim 24 wherein the linker is a disulfide bond.

29. A method of preventing excessive cell proliferation in the eye, comprising contacting the eye with a cell proliferation-inhibiting amount of the composition according to any one of claims 1-28 wherein: the inhibited cells are epithelial cells, endothelial cells, fibroblast cells or keratocytes.

30. A method of treating cancer, comprising contacting the cancer cells with the composition according to any one of claims 1-28 in an amount sufficient for inhibiting proliferation of the cancer cells.

31. A method of treating smooth muscle cell hyperplasia, comprising contacting the smooth muscle cells with the composition according to any one of claims 1-28 in an amount sufficient for inhibiting hyperplasia of smooth muscle cells.

32. A pharmaceutical composition having the formula: receptor-binding internalized ligand-cytocide-encoding agent nucleic acid binding domain, wherein: receptor-binding internalized ligand is a polypeptide reactive with a cell surface receptor; cytocide-encoding agent is a nucleic acid molecule encoding a cytocide, the agent being **conjugated** to the receptor-binding internalized ligand; and wherein the cytocide-encoding agent is bound to the nucleic acid binding domain; and wherein the receptor-binding internalized ligand-cytocide-encoding agent nucleic acid binding domain binds to the cell surface receptor and is internalized in cells bearing the receptor.

33. The composition of claim 32 wherein the receptor binding internalized ligand is a polypeptide reactive with an FGF receptor.

L26 ANSWER 9 OF 25 USPATFULL on STN
2003:200896 Novel co-stimulatory molecules.
Punnonen, Juha, Belmont, CA, UNITED STATES
Lazetic, Alexandra, San Jose, CA, UNITED STATES
Leong, Steven R., Berkeley, CA, UNITED STATES
Chang, Chia-Chun, Los Gatos, CA, UNITED STATES
Apt, Doris, Sunnyvale, CA, UNITED STATES
Gustafsson, Claes, Belmont, CA, UNITED STATES
Maxygen, Inc., Redwood City, CA, UNITED STATES, 94063 (U.S. corporation)
US 2003138881 A1 20030724
APPLICATION: US 2001-32214 A1 20011220 (10)
PRIORITY: US 2000-213946P 20000623 (60)
US 2000-241245P 20001017 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An isolated or recombinant polypeptide comprising an amino acid sequence of an extracellular domain, wherein said extracellular domain amino acid sequence has at least about 75% amino acid sequence identity to an extracellular domain amino acid sequence of at least one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, and is not a naturally-occurring extracellular domain amino acid sequence, and wherein said polypeptide has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1.

2. The isolated or recombinant polypeptide of claim 1, wherein said extracellular domain (ECD) amino acid sequence has at least about 90% sequence identity to an ECD amino acid sequence of at least one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

3. The isolated or recombinant polypeptide of claim 1, which polypeptide comprises an ECD amino acid sequence of any one of SEQ ID NOS:48-68, 174-182, 184-221, 283-285, and 290-293.

4. The isolated or recombinant polypeptide of claim 1, which polypeptide comprises an amino acid sequence of any one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

5. The isolated or recombinant polypeptide of claim 1, wherein the polypeptide has a CD28/CTLA-4 binding affinity ratio greater than the CD28/CTLA-4 binding affinity ratio of human B7-1.

6. The isolated or recombinant polypeptide of claim 1, wherein the polypeptide has either a same binding affinity or an enhanced binding affinity for CD28 as compared to a binding affinity of a wild type co-stimulatory molecule for CD28.

7. The isolated or recombinant polypeptide of claim 1, wherein the polypeptide has a decreased or a lowered binding affinity for CTLA-4 as compared to a binding affinity of a wild type co-stimulatory molecule for CTLA-4.

8. The isolated or recombinant polypeptide of claim 1, 5, 6, or 7, wherein the polypeptide has an ability to induce T-cell proliferation or T-cell activation or both T-cell proliferation and T-cell activation and further comprises at least transmembrane domain (TMD) and/or a cytoplasmic, wherein said transmembrane domain is not a naturally-occurring TMD.

9. The isolated or recombinant polypeptide of claim 1, wherein the polypeptide induces T-cell proliferation.

10. The isolated or recombinant polypeptide of claim 1, 5, 6, or 7, wherein the polypeptide has an ability to induce a T-cell proliferative response about equal to or greater than that of human B7-1.

11. The isolated or recombinant polypeptide of claim 1, wherein the polypeptide has an ability to modulate T-cell activation, but does not induce proliferation of purified T-cells activated by soluble anti-CD3 mAbs.

12. The isolated or recombinant polypeptide of claim 5, which polypeptide comprises an extracellular domain amino acid sequence of any one of SEQ ID NOS:48-68 and 174-209.

13. The isolated or recombinant polypeptide of claim 1, which polypeptide comprises an extracellular domain (ECD) amino acid sequence encoded by an ECD coding nucleotide sequence, the ECD coding nucleotide sequence selected from the group of: (a) a nucleotide sequence comprising a nucleotide fragment of a polynucleotide sequence selected from any of SEQ ID NOS:1-21 and 95-142, wherein said nucleotide fragment encodes an ECD amino acid sequence; (b) a nucleotide sequence that encodes the ECD amino acid sequence of a polypeptide selected from any of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293; and (c) a nucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of a nucleotide sequence (a) or (b).

14. An isolated or recombinant polypeptide, which polypeptide comprises a non-naturally-occurring amino acid sequence encoded by a nucleic acid comprising a polynucleotide sequence selected from the group of: (a) a polynucleotide sequence selected from SEQ ID NOS:1-21 and 95-142, or a complementary polynucleotide sequence thereof; (b) a polynucleotide sequence encoding a polypeptide selected from SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, or a complementary polynucleotide sequence thereof; (c) a polynucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent or highly stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b); (d) a polynucleotide sequence comprising all or a nucleotide fragment of (a), (b), or (c), wherein the nucleotide fragment encodes a polypeptide having a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1; (e) a polynucleotide sequence encoding a polypeptide, the polypeptide comprising an amino acid sequence which is substantially identical over at least about 150 contiguous amino acid residues of any one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293; and (f) a polynucleotide sequence encoding a polypeptide that has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the

CD28/CTLA-4 binding affinity ratio of human B7-1, which polynucleotide sequence has at least about 70% identity to at least one polynucleotide sequence of (a), (b), (c), or (d).

15. The isolated or recombinant polypeptide of claim 14, the polypeptide comprising an amino acid sequence of any one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

16. The isolated or recombinant polypeptide of claim 14, wherein the polypeptide has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1.

17. The isolated or recombinant polypeptide of claim 14 or 16, wherein the polypeptide induces T-cell proliferation.

18. The isolated or recombinant polypeptide of claim 14 or 16, wherein the polypeptide induces a T-cell proliferative response about equal to or greater than that of human B7-1.

19. An isolated or recombinant polypeptide comprising a amino acid sequence according to the formula: MGHTM-X6-W-X8-SLPPK-X14-PCL-X18-X19-X20-QLLVLT-X27-LFYFCSGITPKSVTKRVKETVMLSCDY-X55-TSTE-X60-LTSLRIYW-X69-KDSKMVLAILPGKVQVWPEYKNRTITDMNDN-X101-RIVI-X106-ALR-X110-SD-X113-GTYTCV-X120-QKP-X124-LKGAYKLEHL-X135-SVRLMIRADFPVP-X149-X150-X151-DLGNPSPNIRRLICS-X167-X168-X169-GFPRPHL-X177-WLENGEELNATNTT-X192-SQDP-X197-T-X199-LYMISSEL-X208-FNVTNN-X215-SI-X218-CLIKYGEL-X227-VSQIFPWSKPKQEPPIDQLPF-X249-VIIPVSGALVL-X261-A-X263-VLY-X267-X268-ACRH-X273-ARWKRTRRNEETVGTE RLSPIYLGSAQSSG (SEQ ID NO:284), or a subsequence thereof comprising an extracellular domain, wherein position X6 is Lys or Glu; position X8 is Arg or Gly; position X14 is Arg or Cys; position X18 is Trp or Arg; position X19 is Pro or Leu; position X20 is Ser or Pro; position X27 is Asp or Gly; position X55 is Asn or Ser; position X60 is Glu or Lys; position X69 is Gln or Arg; position X101 is Pro or Leu; position X106 is Leu or Gln; position X110 is Pro or Leu; position X113 is Lys or Ser; position X120 is Val or Ile; position X124 is Val or Asp; position X135 is Thr or Ala; position X149 is Thr, Ser, or del; position X150 is Ile or del; position X151 is Asn or Thr; position X167 is Thr or del; position X169 is Ser or del; position X169 is Gly or del; position X177 is Cys or Tyr; position X192 is Val or Leu; position X197 is Gly or Glu; position X199 is Glu or Lys; position X208 is Gly or Asp; position X215 is His or Arg; position X218 is Ala or Val; position X227 is Ser or Leu; position X249 is Trp, Leu, or Arg; position X261 is Ala or Thr; position X263 is Val, Ala, or Ile; position X267 is Arg or Cys; position X268 is Pro or Leu; and position X273 is Gly or Val.

20. The isolated or recombinant polypeptide of claim 19, which polypeptide comprises an extracellular domain amino acid sequence of any one of SEQ ID NOS:51-56, 58, 61, 66, 67, 174-179, 181, 185-187, 189, 192-194, 197, 199, 202, 205, 208, 215, 217, 220, and 285.

21. The isolated or recombinant polypeptide of claim 19, wherein the polypeptide has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1.

22. The isolated or recombinant polypeptide of claim 19 or 21, wherein the polypeptide induces T-cell proliferation.

23. The isolated or recombinant polypeptide of claim 19 or 21, wherein the polypeptide induces a T-cell proliferative response about equal to or greater than that of human B7-1.

24. The isolated or recombinant polypeptide of claim 19, comprising

three or more of: Lys at position X6; Arg at position X8; Arg at position X14; Trp at position X18; Pro at position X19; Ser at position X20; Asp at position X27; Asn at position X55; Leu at position X106; Pro at position X110; Lys at position X113; Val at position X120; Val at position X124; Thr at position X135; Asn at position X151; Cys at position X177; Val at position X192; Gly at position X197; Glu at position X199; Gly at position X208; His at position X215; Ala at position X218; Trp at position X249; Ala at position X261; Val at position X263; Arg at position X267; Pro at position X268; and Gly at position X273.

25. The isolated or recombinant polypeptide of claim 24, comprising three or more of: Arg at position X8; Arg at position X14; Trp at position X18; Pro at position X19; Ser at position X20; Pro at position X110; Val at position X120; Val at position X124; Cys at position X177; Val at position X192; Gly at position X197; Glu at position X199; Gly at position X208; His at position X215; Ala at position X218; Trp at position X249; Ala at position X261; and Val at position X263.

26. The isolated or recombinant polypeptide of claim 25, comprising the extracellular domain amino acid sequence of SEQ ID NO:66 or SEQ ID NO:285.

27. The isolated or recombinant polypeptide of claim 25, comprising the entire amino acid sequence of SEQ ID NO:66 or SEQ ID NO:285.

28. An isolated or recombinant polypeptide comprising a subsequence of an amino acid sequence set forth in any of SEQ ID NOS:48-68, 174-182, 184-221, 283-285, and 290-293, wherein the subsequence is the extracellular domain of said amino acid sequence.

29. The isolated or recombinant polypeptide of claim 1, 14, 19, or 28, further comprising a signal peptide sequence.

30. The polypeptide of claim 29, wherein the signal peptide sequence is selected from the signal peptide sequence set forth in any of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

31. The polypeptide of claim 30, further comprising a transmembrane domain amino acid sequence or a cytoplasmic domain amino acid sequence selected from the transmembrane domain amino acid sequence or the cytoplasmic domain amino acid sequence set forth in any of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

32. The polypeptide of claim 1, 14, 19, or 28 comprising a soluble extracellular domain, wherein said polypeptide or ECD thereof binds CD28 and/or CTLA-4.

33. The polypeptide of claim 1, 14, 19, 28, 29, or 31, wherein the polypeptide comprises a fusion protein comprising at least one additional amino acid sequence.

34. The polypeptide of claim 33, wherein the at least one additional amino acid sequence comprises at least one Ig polypeptide.

35. The polypeptide of claim 34, wherein the at least one Ig polypeptide comprises at least one human IgG polypeptide comprising an Fc hinge, a CH2 domain, and a CH3 domain.

36. The polypeptide of claim 1, 14, 19, 28, 29, or 31, comprising a polypeptide purification subsequence.

37. The polypeptide of claim 36, wherein the polypeptide purification subsequence is selected from: an epitope tag, a FLAG tag, a polyhistidine sequence, and a GST fusion.

38. The polypeptide of claim 1, 14, 19, 28, 29, or 31 comprising a modified amino acid.

39. The polypeptide of claim 38, wherein the modified amino acid is selected from: a glycosylated amino acid, a **PEGylated** amino acid, a farnesylated amino acid, an acetylated amino acid, a biotinylated amino acid, an amino acid **conjugated** to a lipid moiety, and an amino acid **conjugated** to an organic derivatizing agent.

40. A composition comprising at least one polypeptide of claim 38 and a pharmaceutically acceptable excipient.

41. A composition comprising at least one polypeptide of claim 1, 14, 19, 28, 29, or 31 and a pharmaceutically acceptable excipient.

42. A composition comprising: an isolated or recombinant polypeptide comprising an amino acid sequence selected from the group of SEQ ID NOS:48-68, 174-221, 283-285, 290-293, or a costimulatory fragment thereof, wherein said polypeptide or costimulatory fragment has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1 or an ability to induce a T cell proliferation response equal to or greater than that induced by human B7-1, and a carrier.

43. An isolated or recombinant nucleic acid comprising a polynucleotide sequence selected from: (a) a polynucleotide sequence selected from SEQ ID NOS:1-21 and 95-142, or a complementary polynucleotide sequence thereof; (b) a polynucleotide sequence encoding a polypeptide selected from SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, or a complementary polynucleotide sequence thereof; (c) a polynucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b); and (d) a polynucleotide sequence comprising all or a nucleotide fragment of (a), (b), or (c), wherein the nucleotide fragment encodes a polypeptide having a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1 or a polypeptide having an ability to induce a T cell proliferation response that is about equal to or greater than that induced by human B7-1.

44. An isolated or recombinant nucleic acid comprising a polynucleotide sequence encoding a polypeptide, wherein the encoded polypeptide comprises an amino acid sequence which is substantially identical over at least about 150 contiguous amino acid residues of any one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293 and is a non naturally-occurring amino acid sequence.

45. The nucleic acid of claim 44, wherein the encoded polypeptide is substantially identical over at least about 175 contiguous amino acid residues of any one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

46. An isolated or recombinant nucleic acid comprising a nucleotide sequence coding for a polypeptide comprising the amino acid sequence set forth in any of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, or a subsequence thereof, wherein the subsequence comprises at least one of: the signal sequence of said polypeptide, the extracellular domain of said polypeptide, the transmembrane domain of said polypeptide, and the cytoplasmic domain of said polypeptide, and wherein the amino acid

sequence or subsequence is a non naturally-occurring sequence.

47. The nucleic acid of claim 43, 44, or 46, wherein the polypeptide has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1 or an ability to induce a T cell proliferation response equal to or greater than that of human B7-1.

48. The nucleic acid of claim 43, 44, or 46, wherein the polypeptide has either a same binding affinity or an enhanced binding affinity for CD28 as compared to a binding affinity of a wild type co-stimulatory molecule for CD28.

49. The nucleic acid of claim 43, 44, or 46, wherein the encoded polypeptide has a decreased or a lowered binding affinity for CTLA-4 as compared to a binding affinity of a wild type co-stimulatory molecule for CTLA-4.

50. The nucleic acid of claim 43, 44, 46, or 49, wherein the encoded polypeptide induces T-cell proliferation or T-cell activation or both T-cell proliferation and T-cell activation.

51. The nucleic acid of claim 43, 44, or 46, wherein the encoded polypeptide modulates T-cell activation, but does not induce proliferation of purified T-cells activated by soluble anti-CD3 mAbs.

52. The nucleic acid of claim 43, 44, or 46, wherein the nucleic acid encodes a fusion protein comprising at least one additional amino acid sequence.

53. The nucleic acid of claim 52, wherein the at least one additional amino acid sequence comprises at least one Ig polypeptide.

54. The nucleic acid of claim 53, wherein the at least one Ig polypeptide comprises at least one human IgG polypeptide comprising an Fc hinge, a CH2 domain, and a CH3 domain.

55. The nucleic acid of claim 43, 44, or 46, wherein the encoded polypeptide comprises a signal sequence.

56. The nucleic acid of claim 43, 44, 46, or 49, wherein the encoded polypeptide comprises a precursor peptide.

57. The nucleic acid of claim 43, 44, or 46, wherein the encoded polypeptide comprises an epitope tag sequence.

58. A cell comprising the nucleic acid of claim 43, 44, 46, or 49.

59. The cell of claim 58, wherein the cell expresses a polypeptide encoded by the nucleic acid.

60. A vector comprising the nucleic acid of claim 43, 44, 46, or 49.

61. The vector of claim 60, wherein the vector comprises a plasmid, a cosmid, a phage, a virus, a virus-like particle, or a fragment of a virus.

62. The vector of claim 60, wherein the vector is an expression vector.

63. The expression vector of claim 62, wherein the nucleic acid is operably linked to a promoter.

64. The expression vector of claim 62, further comprising a polynucleotide sequence encoding an antigen.

65. The expression vector of claim 64, wherein the antigen is a cancer antigen.

66. The expression vector of claim 64, wherein the nucleic acid is operably linked to first promoter and the polynucleotide sequence encoding the antigen is operably linked to a second promoter.

67. The expression vector of claim 65, wherein the cancer antigen is EpCam/KSA or a mutant or variant thereof.

68. The expression vector of claim 67, wherein the expression vector comprises the vector shown in FIG. 22B.

69. A host cell comprising the vector of claim 60.

70. A composition comprising the nucleic acid of claim 43, 44, 46, or 49 and an excipient.

71. The composition of claim 70, wherein the excipient is a pharmaceutically acceptable excipient.

72. A composition of matter comprising at least one nucleic acid of claim 43, 44, 46, or 49.

73. The composition of claim 72, wherein the composition comprises a library comprising at least about 2, 5, 10, 50 or more nucleic acids.

74. A composition produced by cleaving at least one nucleic acid of claim 43, 44, or 46.

75. The composition of claim 74, wherein the cleaving comprises mechanical, chemical, or enzymatic cleavage.

76. The composition of claim 75, wherein the enzymatic cleavage comprises cleavage with a restriction endonuclease, an RNAse, or a DNAse.

77. A composition produced by a process comprising incubating at least one nucleic acid of claim 43, 44, or 46 in the presence of deoxyribonucleotide triphosphates and a nucleic acid polymerase.

78. The composition of claim 77, wherein the nucleic acid polymerase is a thermostable polymerase.

79. An isolated or recombinant nucleic acid encoding a polypeptide that has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1, produced by mutating or recombining at least one nucleic acid of claim 43, 44, or 46.

80. An isolated or recombinant polypeptide comprising an amino acid sequence having at least about 95% identity to at least about one of SEQ ID NOS:69-92, 222-252, 286-289, or a subsequence thereof comprising an extracellular domain, wherein said amino acid sequence (a) is a non naturally-occurring amino acid sequence, and (b) comprises at least one of: Gly at position 2; Thr at position 4; Arg at position 5; Gly at position 8; Pro at position 12; Met at position 25; Cys at position 27; Pro at position 29; Leu at position 31; Arg at position 40; Leu at position 52; His at position 65; Ser at position 78; Asp at position 80;

Tyr at position 87; Lys at position 120; Asp at position 122; Lys at position 129; Met at position 135; Phe at position 150; Ile at position 160; Ala at position 164; His at position 172; Phe at position 174; Leu at position 176; Asn at position 178; Asn at position 186; Glu at position 194; Gly at position 196; Thr at position 199; Ala at position 210; His at position 212; Arg at position 219; Pro at position 234; Asn at position 241; Leu at position 244; Thr at position 250; Ala at position 254; Tyr at position 265; Arg at position 266; Glu at position 273; Lys at position 275; Ser at position 276; an amino acid deletion at position 276; or Thr at position 279, wherein the position number corresponds to that of the human B7-1 amino acid sequence (SEQ ID NO:278), wherein said polypeptide has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1 or an ability to induce a T cell proliferation response that is equal to or less than that of human B7-1.

81. The isolated or recombinant polypeptide of claim 80, wherein said polypeptide comprises an amino acid sequence having at least about 98% identity to at least one of SEQ ID NOS:69-92, 222-252, 286-289, or a subsequence thereof comprising an extracellular domain, said amino acid sequence comprising at least one of: Gly at position 2; Thr at position 4; Arg at position 5; Gly at position 8; Pro at position 12; Met at position 25; Cys at position 27; Pro at position 29; Leu at position 31; Arg at position 40; Leu at position 52; His at position 65; Ser at position 78; Asp at position 80; Tyr at position 87; Lys at position 120; Asp at position 122; Lys at position 129; Met at position 135; Phe at position 150; Ile at position 160; Ala at position 164; His at position 172; Phe at position 174; Leu at position 176; Asn at position 178; Asn at position 186; Glu at position 194; Gly at position 196; Thr at position 199; Ala at position 210; His at position 212; Arg at position 219; Pro at position 234; Asn at position 241; Leu at position 244; Thr at position 250; Ala at position 254; Tyr at position 265; Arg at position 266; Glu at position 273; Lys at position 275; Ser at position 276; an amino acid deletion at position 276; and Thr at position 279, wherein the position number corresponds to that of the human B7-1 amino acid sequence (SEQ ID NO:278).

82. The isolated or recombinant polypeptide of claim 80, wherein said polypeptide comprises an amino acid sequence having at least about 98% identity to at least one of SEQ ID NOS:69-92, 222-252, and 286-289, said amino acid sequence comprising at least one of: Gly at position 2; Gly at position 8; Cys at position 27; His at position 65; Asp at position 80; Asp at position 122; Met at position 135; Phe at position 150; Ala at position 164; Phe at position 174; Asn at position 186; Glu at position 194; Arg at position 219; Thr at position 250; Arg at position 266; Lys at position 275; and Ser at position 276, wherein the amino acid position numbers correspond to that of the human B7-1 amino acid sequence (SEQ ID NO:278).

83. The isolated or recombinant polypeptide of claim 80, wherein said polypeptide comprises an amino acid sequence having at least about 98% identity to an extracellular domain of at least one of SEQ ID NOS:69-92, 222-252, and 286-289, said amino acid sequence comprising at least one of: His at position 65; Asp at position 80; Asp at position 122; Met at position 135; Phe at position 150; Ala at position 164; Phe at position 174; Asn at position 186; Glu at position 194; and Arg at position 219, wherein the amino acid position numbers correspond to that of the human B7-1 amino acid sequence (SEQ ID NO:278).

84. The isolated or recombinant polypeptide of claim 83, wherein said polypeptide comprises an amino acid sequence having at least about 98% identity to an extracellular domain of at least one of SEQ ID NOS:69-92,

222-252, 286-289, said sequence comprising at least two of: His at position 65; Asp at position 80; Asp at position 122; Met at position 135; Phe at position 150; Ala at position 164; Phe at position 174; Asn at position 186; Glu at position 194; and Arg at position 219, wherein the amino acid position numbers correspond to that of the human B7-1 amino acid sequence (SEQ ID NO:278).

85. The isolated or recombinant polypeptide of claim 84, wherein said polypeptide comprises an extracellular domain of any one of SEQ ID NOS:81, 85, 86, 88, 90, and 91.

86. The isolated or recombinant polypeptide of claim 80, which polypeptide comprises an extracellular domain of any one of SEQ ID NOS:69-92, 222-252, and 286-289.

87. The isolated or recombinant polypeptide of claim 80, which polypeptide comprises an amino acid sequence of any one of SEQ ID NOS:69-92, 222-252, and 286-289.

88. The isolated or recombinant polypeptide of claim 80, wherein the polypeptide has a CTLA-4/CD28 binding affinity ratio greater than the CTLA-4/CD28 binding affinity ratio of human B7-1.

89. The isolated or recombinant polypeptide of claim 80, wherein the polypeptide has either a same binding affinity or an enhanced binding affinity for CTLA-4 as compared to a binding affinity of a wild type co-stimulatory molecule for CTLA-4.

90. The isolated or recombinant polypeptide of claim 80, wherein the polypeptide has a decreased or a lowered binding affinity for CD28 as compared to a binding affinity of a wild type co-stimulatory molecule for CD28.

91. The isolated or recombinant polypeptide of claim 80, wherein the polypeptide inhibits T-cell proliferation or T-cell activation or both T-cell proliferation and T-cell activation.

92. The isolated or recombinant polypeptide of claim 80, wherein the polypeptide inhibits T-cell proliferation.

93. The isolated or recombinant polypeptide of claim 80, wherein the polypeptide induces a T-cell response less than that of human B7-1.

94. The isolated or recombinant polypeptide of claim 80, wherein the polypeptide modulates T-cell activation, but does not induce proliferation of purified T-cells activated by soluble anti-CD3 mAbs.

95. The isolated or recombinant polypeptide of claim 84 or 91, which polypeptide comprises an extracellular domain amino acid sequence of any one of SEQ ID NOS:69-92 and 222-247.

96. The isolated or recombinant polypeptide of claim 80 or 91, which polypeptide comprises an extracellular domain amino acid sequence encoded by a coding polynucleotide sequence, the coding polynucleotide sequence selected from the group: (a) an extracellular domain coding sequence of a polynucleotide sequence selected from any of SEQ ID NOS:22-45 and 143-173; (b) a polynucleotide sequence that encodes the extracellular domain of a polypeptide selected from any of SEQ ID NOS:69-92, 222-252, and 286-289; and (c) a polynucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of a polynucleotide sequence (a) or (b).

97. An isolated or recombinant polypeptide comprising an amino acid sequence that differs from a primate B7-1 amino acid sequence in at least one mutation selected from: Ser 12 Pro; Leu 25 Met; Gly 27 Cys; Ser 29 Pro; Lys 40 Arg; His 52 Leu; Tyr 65 His; Glu 122 Asp; Glu 129 Lys; Thr 135 Met; Thr 164 Ala; Ser 174 Phe; Glu 196 Gly; Ala 199 Thr; Thr 210 Ala; Lys 219 Arg; Thr 234 Pro; Asp 241 Asn; Val 254 Ala; Arg 275 Lys; Arg 276 Ser; or Arg 279 Thr; the mutation being indicated comprising a mutation relative to human B7-1 with the amino acid sequence shown in SEQ ID NO:278, wherein said amino acid sequence does not occur in nature, and wherein said polypeptide has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1.

98. The isolated or recombinant polypeptide of claim 97, wherein said amino acid sequence differs from said primate B7-1 sequence in at least two of said mutations.

99. The isolated or recombinant polypeptide of claim 97, wherein said primate B7-1 is human B7-1 (SEQ ID NO:278).

100. The isolated or recombinant polypeptide of claim 99, wherein said sequence differs from the human B7-1 sequence in at least two of said mutations.

101. An isolated or recombinant polypeptide comprising an amino acid sequence, said amino acid sequence having at least about 75% identity to at least one polypeptide sequence of SEQ ID NOS:263-272, or a subsequence thereof comprising the extracellular domain, wherein said amino acid sequence is not a naturally-occurring amino acid sequence, and wherein said polypeptide has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1.

102. An isolated or recombinant polypeptide, which polypeptide comprises a non naturally-occurring amino acid sequence encoded by a nucleic acid comprising a polynucleotide sequence selected from: (a) a polynucleotide sequence selected from SEQ ID NOS:22-45, 143-173, 253-262, or a complementary polynucleotide sequence thereof; (b) a polynucleotide sequence encoding a polypeptide selected from SEQ ID NOS:69-92, 222-247, 263-272, 286-289, or a complementary polynucleotide sequence thereof; (c) a polynucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under highly stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b); (d) a polynucleotide sequence comprising all or a nucleotide fragment of (a), (b), or (c), wherein the fragment encodes a polypeptide having a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1; (e) a polynucleotide sequence encoding a polypeptide comprising an amino acid sequence that is substantially identical over at least about 150 contiguous amino acid residues of any one of SEQ ID NOS:69-92, 222-247, 263-272, 286-289, and (f) a polynucleotide sequence encoding a polypeptide that has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1, which polynucleotide sequence has at least about 70% identity to at least one polynucleotide sequence of (a), (b), (c), or (d).

103. The isolated or recombinant polypeptide of claim 102, the polypeptide comprising an amino acid sequence of any one of SEQ ID NOS:69-92, 222-247, 263-272, and 286-289.

104. The isolated or recombinant polypeptide of claim 102, wherein the

polypeptide has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1.

105. The isolated or recombinant polypeptide of claim 102, wherein the polypeptide inhibits T-cell proliferation.

106. The isolated or recombinant polypeptide of claim 102, wherein the polypeptide induces a T-cell response less than that of human B7-1.

107. An isolated or recombinant polypeptide comprising an amino acid sequence according to the formula: MGHTIRRQGTSP-X12-KCPYLKFFQLLV-X25-ACL-X29-HILCSGVHIHVT-X40-EVKEVATLSCGLNVSVEELAQTRIHWQKEKKMVLTM MSGDMNIWPEYKNRTIFDITNNLSIVILALRPSDEGTYECVVLKY-X122-KDAFKR-X129-HLAEVMLSVKAD FPTPSITDFEIPPSNIRRIICS-X164-SGGFPEPHLFWLENGEELNAINTVSQDPET-X196-LYTVSSKLDFNM TANHSFMCLI-X219-YGHLRVNQTFNWNTPKQEHIFP-X241-NLLPSWA ITLISANGIFVICCLTYRFAPRCRERKSNETLRRESVCPV (SEQ ID NO:287), or a subsequence thereof comprising the extracellular domain, wherein position X12 is Ser or Pro; position X25 is Leu or Met; position X29 is Ser or Pro; position X40 is Lys or Arg; position X122 is Glu or Asp; position X129 is Glu or Lys; position X164 is Thr or Ala; position X196 is Glu or Gly; position X219 is Lys or Arg; and position X241 is Asp or Asn.

108. The isolated or recombinant polypeptide of claim 107, which polypeptide comprises the extracellular domain of SEQ ID NO:288 or SEQ ID NO:289.

109. The isolated or recombinant polypeptide of claim 107, comprising the sequence SEQ ID NO:288 or SEQ ID NO:289.

110. The isolated or recombinant polypeptide of claim 107, wherein the polypeptide has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1.

111. The isolated or recombinant polypeptide of claim 107 or 110, wherein the polypeptide inhibits T-cell proliferation.

112. The isolated or recombinant polypeptide of claim 107 or 110, wherein the polypeptide induces a T-cell response less than that of human B7-1.

113. An isolated or recombinant polypeptide comprising a subsequence of an amino acid sequence set forth in any of SEQ ID NOS:69-92, 222-247, 263-272, and 286-289, wherein the subsequence is the extracellular domain of said amino acid sequence.

114. The isolated or recombinant polypeptide of claim 80, 97, 101, 102, 107, or 113, comprising a signal sequence.

115. The polypeptide of claim 114, wherein the signal sequence is selected from the signal sequence set forth in any of SEQ ID NOS:69-92, 222-247, 263-272, and 286-289.

116. The polypeptide of claim 80, 97, 101, 102, 107, or 113, comprising a transmembrane domain sequence or a cytoplasmic domain sequence, selected from the transmembrane domain sequence or the cytoplasmic domain sequence set forth in any of SEQ ID NOS:69-92, 222-247, 263-272, and 286-289.

117. The polypeptide of claim 80, 97, 101, 102, 107, or 113 comprising a soluble extracellular domain.

118. The polypeptide of claim 80, 97, 101, 102, 107, or 113, wherein the polypeptide comprises a fusion protein comprising at least one additional amino acid sequence.

119. The polypeptide of claim 118, wherein the at least one additional amino acid sequence comprises at least one Ig polypeptide.

120. The polypeptide of claim 119, wherein the at least one Ig polypeptide comprises a human IgG polypeptide comprising an Fc hinge, a CH2 domain, and a CH3 domain.

121. The polypeptide of claim 80, 97, 101, 102, 107, or 113, comprising a polypeptide purification subsequence.

122. The polypeptide of claim 121, wherein the polypeptide purification subsequence is selected from: an epitope tag, a FLAG tag, a polyhistidine sequence, and a GST fusion.

123. The polypeptide of claim 80, 97, 101, 102, 107, or 113, comprising a modified amino acid.

124. The polypeptide of claim 123, wherein the modified amino acid is selected from the group consisting of: a glycosylated amino acid, a **PEGylated** amino acid, a farnesylated amino acid, an acetylated amino acid, a biotinylated amino acid, an amino acid **conjugated** to a lipid moiety, and an amino acid **conjugated** to an organic derivatizing agent.

125. A composition comprising at least one polypeptide of claim 124 and a pharmaceutically acceptable excipient.

126. A composition comprising at least one polypeptide of claim 80, 97, 101, 102, 107, or 113, and a pharmaceutically acceptable excipient.

127. A composition comprising: an isolated or recombinant polypeptide comprising the amino acid sequence of SEQ ID NOS:69-92, 222-247, 263-272, 286-289, or a costimulatory fragment thereof, wherein said costimulatory fragment has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1, and a carrier.

128. An isolated or recombinant nucleic acid comprising a polynucleotide sequence selected from: (a) a polynucleotide sequence selected from SEQ ID NOS:22-45, 143-173, or a complementary polynucleotide sequence thereof; (b) a polynucleotide sequence encoding a polypeptide selected from SEQ ID NOS:69-92, 222-247, 286-289, or a complementary polynucleotide sequence thereof; (c) a polynucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under highly stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b); and (d) a polynucleotide sequence comprising all or a nucleotide fragment of (a), (b), or (c); wherein (c) or (d) encodes a polypeptide having a non naturally-occurring amino acid sequence comprising at least one of: Gly at position 2; Thr at position 4; Arg at position 5; Gly at position 8; Pro at position 12; Met at position 25; Cys at position 27; Pro at position 29; Leu at position 31; Arg at position 40; Leu at position 52; His at position 65; Ser at position 78; Asp at position 80; Tyr at position 87; Lys at position 120; Asp at position 122; Lys at position 129; Met at position 135; Phe at position 150; Ile at position 160; Ala at position 164; His at position 172; Phe at position 174; Leu at position 176; Asn at position 178; Asn at position 186; Glu at position 194; Gly at position 196; Thr at position 199; Ala at position 210; His at position 212; Arg at position 219; Pro at position 234; Asn at position 241; Leu at

position 244; Thr at position 250; Ala at position 254; Tyr at position 265; Arg at position 266; Glu at position 273; Lys at position 275; Ser at position 276; an amino acid deletion at position 276; and Thr at position 279, wherein the number of the amino acid position corresponds to that of the human B7-1 amino acid sequence (SEQ ID NO:278), and wherein said polypeptide has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1 and/or an ability to induce a T cell proliferation response that is about equal to or greater than that induced by human B7-1.

129. An isolated or recombinant nucleic acid comprising a polynucleotide sequence selected from: (a) a polynucleotide sequence selected from SEQ ID NOS:253-262, or a complementary polynucleotide sequence thereof; (b) a polynucleotide sequence encoding a polypeptide selected from SEQ ID NOS:263-272, or a complementary polynucleotide sequence thereof; (c) a polynucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under highly stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b) and encodes a polypeptide having a non naturally-occurring sequence; and (d) a polynucleotide sequence comprising all or a nucleotide fragment of (a), (b), or (c), wherein the fragment encodes a polypeptide having (i) a non naturally-occurring sequence and (ii) a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1.

130. An isolated or recombinant nucleic acid comprising a polynucleotide sequence encoding a polypeptide, the encoded polypeptide comprising an amino acid sequence which is substantially identical over at least about 150 contiguous amino acid residues of any one of SEQ ID NOS:69-92, 222-247, 263-272, and 286-289.

131. The nucleic acid of claim 44, wherein the encoded polypeptide is substantially identical over at least about 200 contiguous amino acid residues of any one of SEQ ID NOS:69-92, 222-247, 263-272, and 286-289.

132. An isolated or recombinant nucleic acid comprising a nucleotide sequence coding for a polypeptide comprising the amino acid sequence set forth in any of SEQ ID NOS:69-92, 222-247, 263-272, and 286-289, or a subsequence thereof, wherein the subsequence comprises at least one of: the signal peptide sequence of said polypeptide, the extracellular domain of said polypeptide, the transmembrane domain of said polypeptide, and the cytoplasmic domain of said polypeptide, and wherein the amino acid sequence or subsequence is a non naturally-occurring amino acid sequence.

133. The nucleic acid of claim 128, 129, 130, or 132, wherein the polypeptide has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1.

134. The nucleic acid of claim 128, 129, 130, or 132, wherein the polypeptide has either a same binding affinity or an enhanced binding affinity for CD28 as compared to a binding affinity of a wild type co-stimulatory molecule for CD28.

135. The nucleic acid of claim 128, 129, 130, or 132, wherein the encoded polypeptide has a decreased or a lowered binding affinity for CTLA-4 as compared to a binding affinity of a wild type co-stimulatory molecule for CTLA-4.

136. The nucleic acid of claim 128, 129, 130, or 132, wherein the encoded polypeptide inhibits T-cell proliferation or T-cell activation or both T-cell proliferation and T-cell activation.

137. The nucleic acid of claim 128, 129, 130, or 132, wherein the encoded polypeptide modulates T-cell activation, but does not induce proliferation of purified T-cells activated by soluble anti-CD3 mAbs.

138. The nucleic acid of claim 128, 129, 130, or 132, wherein the nucleic acid encodes a fusion protein comprising at least one additional amino acid sequence.

139. The nucleic acid of claim 138, wherein the at least one additional amino acid sequence comprises at least one Ig polypeptide.

140. The nucleic acid of claim 139, wherein the at least one Ig polypeptide comprises a human IgG polypeptide comprising an Fe hinge, a CH2 domain, and a CH3 domain.

141. The nucleic acid of claim 128, 129, 130, or 132, wherein the encoded polypeptide comprises a signal peptide sequence.

142. The nucleic acid of claim 128, 129, 130, or 132, wherein the encoded polypeptide comprises a precursor peptide.

143. The nucleic acid of claim 128, 129, 130, or 132, wherein the encoded polypeptide comprises an epitope tag sequence.

144. A cell comprising the nucleic acid of claim 128, 129, 130, or 132.

145. The cell of claim 144, wherein the cell expresses a polypeptide encoded by the nucleic acid.

146. A vector comprising the nucleic acid of claim 128, 129, 130, 132, 133, or 136.

147. The vector of claim 146, wherein the vector comprises a plasmid, a cosmid, a phage, a virus, a virus-like particle, or a fragment of a virus.

148. The vector of claim 146, wherein the vector is an expression vector.

149. The expression vector of claim 148, wherein the nucleic acid is operably linked to a promoter.

150. The expression vector of claim 149, further comprising a polynucleotide sequence encoding at least one Ig polypeptide or fragment thereof.

151. The expression vector of claim 150, wherein the at least one Ig polypeptide is a human IgG polypeptide comprising an Fc hinge, a CH2 domain, and a CH3 domain.

152. The expression vector of claim 150, wherein the promoter is a CMV promoter.

153. The expression vector of claim 150, further comprising a BGH polyA sequence.

154. A host cell comprising the vector of claim 146.

155. A composition comprising the nucleic acid of claim 128, 129, 130, or 132, and an excipient.

156. The composition of claim 155, wherein the excipient is a pharmaceutically acceptable excipient.

157. A composition of matter comprising at least one nucleic acid of claim 128, 129, 130, 132, 133, or 136.

158. The composition of claim 157, wherein the composition comprises a library comprising at least about 2, 5, 10, 50 or more nucleic acids.

159. A composition produced by cleaving at least one nucleic acid of claim 128, 129, 130, or 132.

160. The composition of claim 159, wherein the cleaving comprises mechanical, chemical, or enzymatic cleavage.

161. The composition of claim 160, wherein the enzymatic cleavage comprises cleavage with a restriction endonuclease, an RNAse, or a DNAse.

162. A composition produced by a process comprising incubating at least one nucleic acid of claim 128, 129, 130, or 132 in the presence of deoxyribonucleotide triphosphates and a nucleic acid polymerase.

163. The composition of claim 162, wherein the nucleic acid polymerase is a thermostable polymerase.

164. An isolated or recombinant nucleic acid encoding a polypeptide that has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1, produced by mutating or recombining at least one nucleic acid of claim 128, 129, 130, or 132.

165. An isolated or recombinant polypeptide comprising an amino acid sequence according to the formula: MGHTMKWGSLPPKRPCLWLSQLLVLTGLFYFCSGIT PK SVTKRVKETVM-X50-SCDY-X55-X56-STEELTSLRIYWQKDSKMVL AILPGKVQVWPEYKNRTITD MNDNPRIVILALRLSD-X113-GTYTCV-X120-QK-X123-X124-X125-X126-G-X128-X129-X130-X13 1-EHL-X135-SV-X138-L-X140-IRADFPVPSITDIGHPAPNVK RIRCSASG-X170-FPEPRLAWMEDGEEL NAVNTTV-X193-X194-X195-LDTELYSVSSELD-X209-N-X211-TNNHSIVCLIKYGELSVSQIFPWSKPK QEPPIDQLPFWVI-X252-X253-VSGALVLTAVVLYCLACRHVAR (SEQ ID NO:290), or a subsequence thereof comprising the extracellular domain, wherein position X50 is Leu or Pro; position X55 is Asn or Ser; position X56 is Ala or Thr; position X113 is Ser or Lys; position X120 is Ile or Val; position X123 is Pro or deleted; position X124 is Val, Asn, or Asp; position X125 is Leu or Glu; position X126 is Lys or Asn; position X128 is Ala or Ser; position X129 is Tyr or Phe; position X130 is Lys or Arg; position X131 is Leu or Arg; position X135 is Ala or Thr; position X138 is Arg or Thr; position X140 is Met or Ser; position X170 is Asp or Gly; position X193 is Asp or is deleted; position X194 is Gln or is deleted; position X195 is Asp or is deleted; position X211 is Val or Ala; position X252 is Ile or Val; and position X253 is Leu or Pro.

166. The isolated or recombinant polypeptide of claim 165, which polypeptide comprises an amino acid sequence of any one of SEQ ID NOS:59, 62, 180, 184, 188, 195, 196, 200, 201, 204, 211, 213, 219, and 291.

167. An isolated or recombinant polypeptide comprising an amino acid sequence according to the formula: MGHTMKWG-X9-LPPKRPCLWLSQLLVLTGLFYFCSG-X35-TPKSVTKRV KETVMLSCDY-X55-TSTEELTSLRIYWQKDSKMVLAILPGKVQVW PEYKNRTITDMNDNPRIVILALR-X110-SDSGTYTCVIQKP-X124-LKGAYKLEHL-X135-SVRLMIRADFPVPTINDLGNPSPNIRRLICSTSGGFP

RPHLYWLENG-X183-ELNATNTT-X192-SQDPETKLYMISSELDFN-X211-TSN-X215-X216-X217-LCLVKYGDLTVSQ-X231-FYWQESKPTPSANQHLTWTIIIPVSAFGISVIIAVI LTCLTCRNAAIRRQRRENEV-X288-M-X290-SCSQSP (SEQ ID NO:292), or a subsequence thereof comprising the extracellular domain, wherein position X9 is Thr or Ser; position X35 is Ile or Thr; position X55 is Asn or Ser; position X110 is Leu or Pro; position X124 is Asp or Val; position X135 is Thr or Ala; position X183 is Lys or Glu; position X192 is Leu or Val; position X211 is Met or Thr; position X215 is His or is deleted; position X216 is Ser or is deleted; position X217 is Phe or is deleted; position X231 is Thr or Ser; position X288 is Lys or Glu; position X290 is Glu or Gln, and wherein said sequence is a non naturally-occurring sequence.

168. The isolated or recombinant polypeptide of claim 167, which polypeptide comprises an amino acid sequence of any one of SEQ ID NOS:48, 182, 183, 212, 214, 216, 218, 221, and 293.

169. An isolated or recombinant polypeptide comprising the sequence SEQ ID NO:93, SEQ ID NO:94, or a subsequence thereof, wherein the subsequence comprises at least one of: the signal peptide of said polypeptide, the extracellular domain of said polypeptide, the transmembrane domain of said polypeptide, and the cytoplasmic domain of said polypeptide.

170. An isolated or recombinant nucleic acid comprising a polynucleotide sequence selected from: (a) a polynucleotide sequence selected from SEQ ID NO:46, SEQ ID NO:47, or a complementary polynucleotide sequence thereof; (b) a polynucleotide sequence encoding a polypeptide selected from SEQ ID NO:93, SEQ ID NO:94, or a complementary polynucleotide sequence thereof; (c) a polynucleotide sequence encoding a subsequence of a polypeptide selected from SEQ ID NO:93, SEQ ID NO:94, or a complementary polynucleotide sequence thereof, wherein the subsequence comprises at least one of: the signal peptide of said polypeptide, the extracellular domain of said polypeptide, the transmembrane domain of said polypeptide, and the cytoplasmic domain of said polypeptide.

171. A polypeptide which is specifically bound by a polyclonal antisera raised against at least one antigen, the at least one antigen comprising the sequence SEQ ID NOS:48-94, 174-252, 263-272, 283-293, or a fragment thereof, wherein the antisera is subtracted with a polypeptide encoded by one or more of GenBank Nucleotide Accession Nos: A92749, A92750, AA983817, AB026121, AB030650, AB030651, AB038153, AF010465, AF065893, AF065894, AF065895, AF065896, AF079519, AF106824, AF106825, AF106828, AF106829, AF106830, AF106831, AF106832, AF106833, AF106834, AF203442, AF203443, AF216747, AF257653, AH004645, AH008762, AX000904, AX000905, D49843, L12586, L12587, M27533, M83073, M83074, M83075, M83077, NM005191, S74541, S74540, S74695, S74696, U05593, U10925, U19833, U19840, U26832, U33063, U33208, U57755, U88622, X60958, Y08823, and Y09950.

172. An antibody or antisera produced by administering the polypeptide of claim 1, 80, 101, or 169 to a mammal, which antibody or antisera specifically binds at least one antigen, the at least one antigen comprising a polypeptide comprising one or more of the amino acid sequences SEQ ID NOS:48-94, 174-252, 263-272, and 283-293, which antibody or antisera does not specifically bind to a polypeptide encoded by one or more of GenBank Nucleotide Accession Nos: A92749, A92750, AA983817, AB026121, AB030650, AB030651, AB038153, AF010465, AF065893, AF065894, AF065895, AF065896, AF079519, AF106824, AF106825, AF106828, AF106829, AF106830, AF106831, AF106832, AF106833, AF106834, AF203442, AF203443, AF216747, AF257653, AH004645, AH008762, AX000904, AX000905, D49843, L12586, L12587, M27533, M83073, M83074, M83075, M83077,

NM005191, S74541, S74540, S74695, S74696, U05593, U10925, U19833, U19840, U26832, U33063, U33208, U57755, U88622, X60958, Y08823, and Y09950.

173. An antibody or antisera which specifically binds a polypeptide, the polypeptide comprising an amino acid sequence selected from: SEQ ID NOS:48-94, 174-252, 263-272, and 283-293, wherein the antibody or antisera does not specifically bind to a polypeptide encoded by one or more of GenBank Nucleotide Accession Nos: A92749, A92750, AA983817, AB026121, AB030650, AB030651, AB038153, AF010465, AF065893, AF065894, AF065895, AF065896, AF079519, AF106824, AF106825, AF106828, AF106829, AF106830, AF106831, AF106832, AF106833, AF106834, AF203442, AF203443, AF216747, AF257653, AH004645, AH008762, AX000904, AX000905, D49843, L12586, L12587, M27533, M83073, M83074, M83075, M83077, NM005191, S74541, S74540, S74695, S74696, U05593, U10925, U19833, U19840, U26832, U33063, U33208, U57755, U88622, X60958, Y08823, and Y09950.

174. A method of producing a polypeptide, the method comprising: (a) introducing into a population of cells a nucleic acid of claim 43, 46, 128, 129, 132, or 170, the nucleic acid operatively linked to a regulatory sequence effective to produce the encoded polypeptide; (b) culturing the cells in a culture medium to produce the polypeptide; and (c) isolating the polypeptide from the cells or from the culture medium.

175. A method of producing a polypeptide, the method comprising (a) introducing into a population of cells a recombinant expression vector comprising the nucleic acid of claim 43, 46, 128, 129, 132, or 170; (b) culturing the cells in a culture medium to produce the polypeptide encoded by the expression vector; and (c) isolating the polypeptide from the cells or from the culture medium.

176. A method of producing a polypeptide, the method comprising: (a) introducing into a population of cells a recombinant expression vector comprising the nucleic acid of claim 43, 46, 128, 129, 132, or 170; (b) administering the expression vector into a mammal; and (c) isolating the polypeptide from the mammal or from a byproduct of the mammal.

177. A method of inducing T-cell proliferation, the method comprising: contacting a population of T cells with a polypeptide of claim 1, 80, 101, or 169, thereby inducing proliferation of the T cells.

178. A method of inhibiting T-cell proliferation, the method comprising: contacting a population of T cells with a polypeptide of claim 1, 80, 101, or 169, thereby inhibiting proliferation of the T cells.

179. A method of modifying T-cell proliferation, the method comprising: contacting a population of T cells with a polypeptide of claim 1, 80, 101, or 169, thereby modifying proliferation of the T cells.

180. A method of modifying T-cell activation, the method comprising: contacting a population of T cells with a polypeptide of claim 1, 80, 101, or 169, thereby modifying activation of the T cells.

181. The method of claim 177, 178, 179, or 180 wherein the T cells are in culture.

182. A method of treating an autoimmune disorder or medical condition in a subject, the method comprising: administering to the subject an effective amount of the polypeptide of claim 1, 80, 101, or 169.

183. A method of treating an autoimmune disorder or medical condition in a subject, the method comprising: administering to the subject an

effective amount of an expression vector comprising the nucleic acid of claim 43, 46, 128, 129, 132, or 170

184. The method of claim 182, wherein the autoimmune disorder or medical condition is selected from the group comprising: multiple sclerosis, rheumatoid arthritis, lupus erythematosus, psoriasis, and type I diabetes.

185. The method of claim 182, wherein the medical condition comprises an allogeneic or xenogeneic graft or transplant.

186. A method of treating a medical disorder in a subject, the method comprising: administering to the subject an effective amount of the polypeptide of claim 1, 80, 101, or 169.

187. The method of claim 186, wherein the medical disorder comprises: cancer, viral infection (e.g. **HIV**), or bacterial infection.

188. In a method of treating a disorder treatable by administration of a co-stimulatory molecule to a subject, an improved method comprising: administering to the subject an effective amount of the polypeptide of claim 1, 80, 101, or 169.

189. The method of claim 188, wherein the disorder treatable by administration of a co-stimulatory molecule is selected from the group comprising: sclerosis, rheumatoid arthritis, lupus erythematosus, psoriasis, type I diabetes, allogeneic grafts, xenogeneic grafts, cancer, viral infection, and bacterial infection.

190. A method of recombination, the method comprising recursively recombining one or more nucleic acids of claim 43, 46, 128, 129, 132, or 170, with at least one additional nucleic acid.

191. The method of claim 190, wherein the at least one additional nucleic acid encodes a co-stimulatory homologue or subsequence thereof.

192. The method of claim 190, wherein the recursive recombination produces at least one library of recombinant co-stimulatory homologue nucleic acids.

193. A nucleic acid library produced by the method of claim 192.

194. A population of cells comprising the library of claim 193.

195. A recombinant co-stimulatory homologue nucleic acid produced by the method of claim 191.

196. A cell comprising the nucleic acid of claim 195.

197. The method of claim 190, wherein the recursive recombination is performed in vitro.

198. The method of claim 190, wherein the recursive recombination is performed in vivo.

199. A method of producing a modified co-stimulatory nucleic acid homologue comprising mutating a nucleic acid of claim 43, 46, 128, 129, 132, or 170.

200. The modified co-stimulatory homologue nucleic acid homologue produced by the method of claim 199.

201. A computer or computer readable medium comprising a database comprising a sequence record comprising one or more character strings corresponding to a nucleic acid or polypeptide sequence selected from SEQ ID NOS:1-272 and 283-293.

202. An integrated system comprising a computer or computer readable medium comprising a database comprising one or more sequence records, each of said one or more sequence records comprising one or more character strings corresponding to a nucleic acid or polypeptide sequence selected from SEQ ID NOS:1-272 and 283-293, the integrated system further comprising a user input interface allowing a user to selectively view one or more sequence records.

203. The integrated system of claim 202, the computer or computer readable medium comprising an alignment instruction set which aligns the one or more character strings with one or more additional character strings corresponding to a nucleic acid or polypeptide sequence.

204. The integrated system of claim 203, wherein the instruction set comprises one or more of: a local homology comparison determination, a homology alignment determination, a search for similarity determination, and a BLAST determination.

205. The integrated system of claim 203, further comprising a user readable output element which displays an alignment produced by the alignment instruction set.

206. The integrated system of claim 202, the computer or computer readable medium further comprising an instruction set which translates one or more nucleic acid sequences, each of said one or more nucleic acid sequences comprising a sequence selected from SEQ ID NOS:1-47, 95-173, and 253-262, into an amino acid sequence.

207. The integrated system of claim 202, the computer or computer readable medium further comprising an instruction set for reverse-translating at least one amino acid sequence comprising a sequence selected from SEQ ID NOS:48-94, 174-252, 263-272, and 283-293, into a nucleic acid sequence.

208. The integrated system of claim 207, wherein the instruction set selects the nucleic acid sequence by applying a codon usage instruction set or an instruction set which determines sequence identity to a test nucleic acid sequence.

209. A method of using a computer system to present information pertaining to at least one of a plurality of sequence records stored in a database, said sequence records each comprising one or more character strings corresponding to SEQ ID NOS:1-272 and 283-293, the method comprising: (a) determining a list of one or more character strings corresponding to one or more of SEQ ID NOS:1-272 and 283-293, or a subsequence thereof; (b) determining which character strings of said list are selected by a user; and (c) displaying the selected character strings, or aligning the selected character strings with an additional character string.

210. The method of claim 209, further comprising displaying an alignment of the selected character string with the additional character string.

211. The method of claim 209, further comprising displaying the list.

212. A nucleic acid which comprises a unique subsequence in a nucleic acid selected from SEQ ID NOS:1-47, 95-173, and 253-262, wherein the

unique subsequence is unique as compared to a nucleic acid corresponding to any of GenBank Nucleotide Accession No.: A92749, A92750, AA983817, AB026121, AB030650, AB030651, AB038153, AF010465, AF065893, AF065894, AF065895, AF065896, AF079519, AF106824, AF106825, AF106828, AF106829, AF106830, AF106831, AF106832, AF106833, AF106834, AF203442, AF203443, AF216747, AF257653, AH004645, AH008762, AX000904, AX000905, D49843, L12586, L12587, M27533, M83073, M83074, M83075, M83077, NM005191, S74541, S74540, S74695, S74696, U05593, U10925, U19833, U19840, U26832, U33063, U33208, U57755, U88622, X60958, Y08823, and Y09950.

213. A polypeptide which comprises a unique subsequence in a polypeptide selected from: SEQ ID NOS:48-94, 174-252, 263-272, and 283-293, wherein the unique subsequence is unique as compared to a polypeptide encoded by any of GenBank Nucleotide Accession Nos: A92749, A92750, AA983817, AB026121, AB030650, AB030651, AB038153, AF010465, AF065893, AF065894, AF065895, AF065896, AF079519, AF106824, AF106825, AF106828, AF106829, AF106830, AF106831, AF106832, AF106833, AF106834, AF203442, AF203443, AF216747, AF257653, AH004645, AH008762, AX000904, AX000905, D49843, L12586, L12587, M27533, M83073, M83074, M83075, M83077, NM005191, S74541, S74540, S74695, S74696, U05593, U10925, U19833, U19840, U26832, U33063, U33208, U57755, U88622, X60958, Y08823, and Y09950.

214. A target nucleic acid which, but for the degeneracy of the genetic code, hybridizes under stringent conditions to a unique coding oligonucleotide which encodes a unique subsequence in a polypeptide selected from: SEQ ID NOS:48-94, 174-252, 263-272, and 283-293, wherein the unique subsequence is unique as compared to a polypeptide encoded by any of GenBank Nucleotide Accession No.: A92749, A92750, AA983817, AB026121, AB030650, AB030651, AB038153, AF010465, AF065893, AF065894, AF065895, AF065896, AF079519, AF106824, AF106825, AF106828, AF106829, AF106830, AF106831, AF106832, AF106833, AF106834, AF203442, AF203443, AF216747, AF257653, AH004645, AH008762, AX000904, AX000905, D49843, L12586, L12587, M27533, M83073, M83074, M83075, M83077, NM005191, S74541, S74540, S74695, S74696, U05593, U10925, U19833, U19840, U26832, U33063, U33208, U57755, U88622, X60958, Y08823, and Y09950.

215. The nucleic acid of claim 214, wherein the stringent conditions are selected such that a perfectly complementary oligonucleotide to the coding oligonucleotide hybridizes to the coding oligonucleotide with at least about a 5× higher signal to noise ratio than for hybridization of the perfectly complementary oligonucleotide to a control nucleic acid corresponding to any of GenBank Nucleotide Accession No.: A92749, A92750, AA983817, AB026121, AB030650, AB030651, AB038153, AF010465, AF065893, AF065894, AF065895, AF065896, AF079519, AF106824, AF106825, AF106828, AF106829, AF106830, AF106831, AF106832, AF106833, AF106834, AF203442, AF203443, AF216747, AF257653, AH004645, AH008762, AX000904, AX000905, D49843, L12586, L12587, M27533, M83073, M83074, M83075, M83077, NM005191, S74541, S74540, S74695, S74696, U05593, U10925, U19833, U19840, U26832, U33063, U33208, U57755, U88622, X60958, Y08823, and Y09950, wherein the target nucleic acid hybridizes to the unique coding oligonucleotide with at least about a 2× higher signal to noise ratio as compared to hybridization of the control nucleic acid to the coding oligonucleotide.

216. A method of therapeutic or prophylactic treatment of a disease or disorder in a subject in need of such treatment, comprising: administering to the subject at least one polypeptide of claim 1, 80, 101, or 169 or at least one nucleic acid of claim 43, 46, 128, 129, 132, or 170, and at least one immunogen specific for said disease or disorder, wherein the combined amount of the at least one polypeptide or at least one nucleic acid and the at least one immunogen is effective to prophylactically or therapeutically treat said disease or disorder.

217. The method of claim 216, wherein the at least one polypeptide or nucleic acid is present in an amount sufficient to enhance, diminish, modulate or modify an immune response induced by the at least one immunogen.

218. The method of claim 216, wherein a composition comprising the at least one polypeptide or nucleic acid, the immunogen, and a pharmaceutically acceptable excipient is administered to the subject in an amount effective to treat said disease or disorder.

219. The method of claim 216, wherein the subject is a mammal.

220. The method of claim 219, wherein the mammal is a human.

221. The method of claim 216, wherein the polypeptide is administered in vivo to the subject.

222. The method of claim 216, wherein the polypeptide is administered in vitro or ex vivo to one or more cells of the subject.

223. A method of modulating an immune response in a subject, comprising: administering to the subject a polynucleotide comprising a nucleic acid sequence of claim 43, 46, 128, 129, 132, or 170, operably linked to a promoter sequence that controls the expression of said nucleic acid sequence, said polynucleotide being present in an amount sufficient that uptake of said polynucleotide into one or more cells of the subject occurs and sufficient expression of said nucleic acid sequence results to produce an amount of a polypeptide effective to modulate an immune response.

224. The method of claim 223, further comprising administering to the subject an antigen specific for the disease or disorder, wherein the polynucleotide is administered to the subject in an amount sufficient to modulate the immune response induced in the subject by the antigen.

225. The method of claim 223, wherein the polynucleotide further comprises a nucleotide sequence encoding for an antigen.

226. The method of claim 223, wherein the polynucleotide further comprises at least one additional nucleotide sequence encoding a cytokine, adjuvant, co-stimulatory molecule, or at least one additional nucleotide sequence comprising a promoter.

227. The method of claim 223, wherein the subject is a mammal.

228. The method of claim 227, wherein the mammal is a human.

229. The method of claim 223, wherein said polynucleotide comprises a vector.

230. A method of treating a disease or disorder in a subject in need of such treatment, comprising: administering to the subject at least one polypeptide of claim 1, 80, 101, or 169 or at least one nucleic acid of claim 43, 46, 128, 129, 132, or 170 in an amount effective to treat said disease or disorder.

231. A method of therapeutic or prophylactic treatment of a disease or disorder in a subject in need of such treatment, comprising: administering to the subject a polypeptide of claim 32 or 117 and an immunogen specific for said disease or disorder, wherein the combined amount of polypeptide and immunogen is effective to prophylactically or

therapeutically treat said disease or disorder.

232. The method of claim 231, wherein the polypeptide is present in an amount sufficient to enhance, diminish or modify an immune response induced by the immunogen.

233. The method of claim 231, wherein a composition comprising the polypeptide, the immunogen, and a pharmaceutically acceptable excipient is administered to the subject in an amount effective to treat the disease or disorder.

234. The method of claim 231, wherein the subject is a mammal.

235. The method of claim 234, wherein the mammal is a human.

236. The method of claim 231, wherein the polypeptide is administered in vivo to the subject.

237. The method of claim 231, wherein the polypeptide is administered in vitro or ex vivo to one or more cells of the subject.

238. A method of treating a disease or disorder in a subject in need of such treatment, comprising: administering to the subject a polypeptide of claim 58 in an amount effective to treat the disease or disorder.

239. The isolated or recombinant polypeptide of claim 165, comprising three or more of: Leu at position X50; Asn at position X55; Ala at position X56; Ser at position X113; Ile at position X120; Pro at position X123; Val at position X124; Leu at position X125; Lys at position X126; Ala at position X128; Tyr at position X129; Lys at position X130; Leu at position X131; Ala at position X135; Arg at position X138; Met at position X140; Asp at position X170; Asp at position X193; Asp at position X194; Asp at position X195; Val at position X211; Ile at position X252; and Leu at position X253.

240. The isolated or recombinant polypeptide of claim 167, comprising three or more of: Thr at position X9; Ile at position X35; Asn at position X55; Leu at position X110; Asp at position X124; Thr at position X135; Lys at position X183; Leu at position X192; Met at position X211; His at position X215; Ser at position X216; Phe at position X217; Thr at position X231; Lys at position X288; and Glu at position X290.

241. A method of modulating or altering a T-cell response specific to an antigen in a subject, the method comprising administering to the subject at least one polynucleotide sequence encoding a polypeptide comprising any of SEQ ID NOS:48-94, 174-252, 263-272 and 283-293 or fragment thereof, and a polynucleotide sequence encoding the antigen or antigenic fragment thereof, wherein each of the at least one polynucleotide sequences is expressed in the subject in an amount effective to modulate or alter a T cell response.

242. The method of claim 241, wherein the at least one polynucleotide sequence encoding a polypeptide comprises a polynucleotide sequence selected from any of SEQ ID NOS:1-47, 95-173, and 253-262.

243. The method of claim 241, wherein the polypeptide or fragment thereof interacts with or binds a T cell surface receptor.

244. The method of claim 241, wherein the T-cell response is enhanced.

245. The method of claim 244, wherein the enhanced T cell response is

sufficient to eliminate cells bearing the antigen or antigenic fragment thereof.

246. The method of claim 241, wherein the T-cell response is suppressed or inhibited.

247. The method of claim 241, wherein the antigen or antigenic fragment thereof is an antigen or antigenic fragment thereof of an infectious agent or a cancer.

248. The method of claim 244, wherein the polypeptide comprises SEQ ID NO:66 or the extracellular domain amino acid sequence thereof.

249. The method of claim 245, wherein the polypeptide comprises SEQ ID NO:86 or the extracellular domain amino acid sequence thereof.

250. The method of claim 244, wherein the at least one polynucleotide sequence encoding a NCSM polypeptide or fragment thereof is operably linked to a promoter in a first vector.

251. The method of claim 250, wherein the at least one polynucleotide sequence encoding the antigen or antigenic fragment thereof is operably linked to a promoter in the first vector.

252. The method of claim 250, wherein the at least one polynucleotide sequence encoding the antigen or antigenic fragment thereof is operably linked to a promoter in the a second vector.

253. A vector comprising at least one polynucleotide sequence encoding a polypeptide comprising any of SEQ ID NOS:48-94, 174-252, 263-272 and 283-293 or fragment thereof, and a polynucleotide sequence encoding the antigen or antigenic fragment thereof, wherein the polypeptide or fragment thereof interacts with or binds to a T cell receptor when expressed in a subject, and wherein each of the at least one polynucleotide sequences is operably linked to a promoter for expression in the subject and is present in an amount sufficient that when expressed is effective to modulate or alter a T cell response.

254. The vector of claim 253, wherein the at least one polynucleotide sequence encoding a polypeptide comprises a polynucleotide sequence of any of SEQ ID NOS:1-47, 95-173, and 253-262.

255. The vector of claim 253, wherein each of the at least one polynucleotide sequences is expressed in the subject in an amount effective to enhance a T cell response such that cells expressing the antigen or antigenic fragment thereof are eliminated.

256. The vector of claim 253, wherein each of the at least one polynucleotide sequences is expressed in the subject in an amount effective to inhibit a T cell response.

257. A vector comprising at least one polynucleotide sequence encoding a polypeptide comprising any of SEQ ID NOS:48-94, 174-252, 263-272 and 283-293 or fragment thereof, wherein the polypeptide or fragment thereof interacts with or binds to a T cell receptor when expressed in a subject, wherein the at least one polynucleotide sequence is operably linked to a promoter for expression in the subject and is present in an amount sufficient that when expressed is effective to modulate or alter a T cell response.

258. A method of modulating or altering an immune response in a subject, the method comprising introducing into cells of a tumor of the subject

at least one polynucleotide sequence encoding a polypeptide comprising any of SEQ ID NOS:48-94, 174-252, 263-272 and 283-293 or fragment thereof, wherein the polypeptide or fragment thereof interacts with or binds to a T cell receptor when expressed in a subject, and wherein the at least one polynucleotide sequence is operably linked to a promoter for expression in the subject and is present in an amount sufficient that when expressed is effective to modulate or alter a T cell response.

259. An isolated or recombinant polypeptide comprising an amino acid sequence corresponding to an extracellular domain, wherein said amino acid sequence has at least about 92% amino acid sequence identity to the amino acid sequence corresponding to the extracellular domain of SEQ ID NO:66, and wherein said polypeptide has a CD28/CTLA-4 binding affinity ratio greater than the CD28/CTLA-4 binding affinity ratio of human B7-1.

260. The isolated or recombinant polypeptide of claim 259, further comprising at least one further amino acid sequence corresponding to a signal peptide.

261. The isolated or recombinant polypeptide of claim 260, further comprising at least one further amino acid sequence corresponding to a transmembrane domain or a cytoplasmic domain.

262. The isolated or recombinant polypeptide of claim 259, wherein said extracellular domain amino acid sequence has at least about 95% amino acid sequence identity to an extracellular domain amino acid sequence of SEQ ID NO:66, and wherein said polypeptide has a CD28/CTLA-4 binding affinity ratio greater than the CD28/CTLA-4 binding affinity ratio of human B7-1, and/or an ability to induce a T cell proliferation response at least about equal to or greater than the T cell proliferation response induced by human B7-1.

263. An isolated or recombinant nucleic acid comprising a nucleotide sequence selected from the group of: (a) a nucleotide sequence that encodes an extracellular domain (ECD), said nucleotide sequence comprising an ECD coding subsequence of a polynucleotide sequence selected from the group of SEQ ID NOS:1-21 and 95-142, or a complementary nucleotide sequence thereof; (b) a nucleotide sequence encoding an ECD, said ECD comprising an amino acid subsequence of a polypeptide sequence selected from the group of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, or a complementary nucleotide sequence thereof; and (c) a nucleotide sequence that, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b), wherein said nucleotide sequence encodes a polypeptide that has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1 and/or an ability to induce a T cell proliferation response equal to or greater than that induced by human B7-1.

264. The isolated or recombinant nucleic acid of claim 263, wherein the nucleotide sequence of (c) hybridizes under at least stringent conditions over substantially the entire length of polynucleotide sequence (a) and encodes a polypeptide that has a CD28/CTLA-4 binding affinity ratio greater than the CD28/CTLA-4 binding affinity ratio of human B7-1.

265. The isolated or recombinant nucleic acid of claim 264, further comprising at least a second nucleotide sequence that encodes a signal peptide, wherein said second nucleotide sequence is selected from the group of: (a) a nucleotide sequence comprising a signal peptide coding subsequence of a polynucleotide sequence selected from the group of SEQ

ID NOS:1-21 and 95-142, or a complementary nucleotide sequence thereof; (b) a nucleotide sequence encoding a signal peptide, said signal peptide comprising an amino acid subsequence of a polypeptide sequence selected from the group of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, or a complementary nucleotide sequence thereof; (c) a nucleotide sequence that, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b), wherein said nucleotide sequence encodes a polypeptide that has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1; and (d) a nucleotide sequence encoding a signal peptide of a B7-1 polypeptide.

266. The isolated or recombinant nucleic acid of claim 265, wherein the nucleotide sequence of (c) hybridizes under at least stringent conditions over substantially the entire length of polynucleotide sequence (a) and encodes a polypeptide that has a CD28/CTLA-4 binding affinity ratio greater than the CD28/CTLA-4 binding affinity ratio of human B7-1 or an ability to induce a T cell proliferation response about equal to or greater than that induced by human B7-1.

267. The isolated or recombinant nucleic acid of claim 265, further comprising at least a third nucleotide sequence encoding a transmembrane domain selected from the group of: (a) a nucleotide sequence comprising a transmembrane domain coding subsequence of a polynucleotide sequence selected from the group of SEQ ID NOS:1-21 and 95-142, or a complementary nucleotide sequence thereof; (b) a nucleotide sequence encoding a transmembrane domain, said transmembrane domain comprising an amino acid subsequence of a polypeptide sequence selected from the group of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, or a complementary nucleotide sequence thereof; (c) a nucleotide sequence that, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b), wherein said nucleotide sequence encodes a polypeptide that has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1; and (d) a nucleotide sequence that encodes a transmembrane domain of a B7-1 polypeptide.

268. The isolated or recombinant nucleic acid of claim 267, further comprising at least a fourth nucleotide sequence encoding a cytoplasmic domain selected from the group of: (a) a nucleotide sequence comprising a cytoplasmic domain coding subsequence of a polynucleotide sequence selected from the group of SEQ ID NOS:1-21 and 95-142, or a complementary nucleotide sequence thereof; (b) a nucleotide sequence encoding a cytoplasmic domain, said cytoplasmic domain comprising an amino acid subsequence of a polypeptide sequence selected from the group of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, or a complementary nucleotide sequence thereof; (c) a nucleotide sequence that, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b), wherein said nucleotide sequence encodes a polypeptide that has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1; and (d) a nucleotide sequence that encodes a cytoplasmic domain of a B7-1 polypeptide.

269. An isolated or recombinant polypeptide variant comprising an amino acid sequence that differs from the amino acid sequence of a primate B7-1, wherein the difference between the amino acid sequence of the variant and the amino acid sequence of the primate B7-1 comprises a different amino acid at position 65 other than alanine, wherein the

position corresponds to the position in the amino acid sequence of human B7-1 of SEQ ID NO:278.

270. The isolated or recombinant polypeptide variant of claim 269, wherein the different amino acid is selected from the group of His, Arg, Lys, Pro, Phe, and Trp.

271. The isolated or recombinant polypeptide variant of claim 270, wherein the primate B7-1 is human B7-1 and the different amino acid is histidine.

272. The isolated or recombinant polypeptide variant of claim 271, wherein the variant has a CTLA-4/CD28 binding affinity ratio greater than the CTLA-41CD28 binding affinity ratio of human B7-1.

273. The isolated or recombinant polypeptide variant of claim 271, wherein the variant has an ability to induce a T cell proliferation response that is about equal to or less than the T cell proliferation response induced by human B7-1.

274. An isolated or recombinant polypeptide variant comprising an amino acid sequence that differs from the amino acid sequence of a primate B7-2, wherein the difference between the amino acid sequence of the variant and the amino acid sequence of the primate B7-2 comprises a different amino acid at position 56 of the B7-2 polypeptide sequence shown at GenBank Acc. No. AAA58389 or at position 50 of the B7-2 polypeptide sequence shown at GenBank Acc. No. AAA86473.

275. The isolated or recombinant polypeptide variant of claim 274, wherein the different amino acid is selected from the group of His, Arg, Lys, Pro, and/or Trp.

276. The isolated or recombinant polypeptide variant of claim 275, wherein the primate B7-2 is human B7-2 and the different amino acid is histidine.

277. The isolated or recombinant polypeptide variant of claim 276, wherein the variant has a CTLA-4/CD28 binding affinity ratio greater than the CTLA-4/CD28 binding affinity ratio of human B7-1 or B7-2.

278. The isolated or recombinant polypeptide variant of claim 276, wherein the variant has wherein the variant has an ability to induce a T cell proliferation response that is about equal to or less than the T cell proliferation response induced by human B7-1 or B7-2.

279. An isolated or recombinant polypeptide variant comprising an amino acid sequence that differs from the extracellular domain (ECD) amino acid sequence of a bovine B7-1, wherein the difference between the amino acid sequence of the variant and the ECD amino acid sequence of the bovine B7-1 comprises a different amino acid at one or more of the following amino acid residue positions: position 110, 124, 135, 192, 197, 199, 211, 213, 217, 218, 221, 225, 227, 231, 233, 235, 236, 237, 239, 240, 242, 243, and 244, wherein each position corresponds to the position in the amino acid sequence of bovine B7-1 of SEQ ID NO:280.

280. The isolated or recombinant polypeptide variant of claim 279, wherein the difference between the amino acid sequence of the variant and the ECD amino acid sequence of the bovine B7-1 comprises at least one of: (a) a different amino acid at position 110, wherein the different amino acid is proline; (b) a different amino acid at position 124, wherein the different amino acid is valine; (c) a different amino acid at position 135, wherein the different amino acid is alanine; (d) a

different amino acid at position 192, wherein the different amino acid is valine; (e) a different amino acid at position 197, wherein the different amino acid is glycine; (f) a different amino acid at position 199, wherein the different amino acid is glutamic acid; (g) a different amino acid at position 211, wherein the different amino acid is valine; (h) a different amino acid at position 213, wherein the different amino acid is asparagines; (i) a different amino acid at position 217, wherein the different amino acid is isoleucine; (j) a different amino acid at position 218, wherein the different amino acid is valine; (k) a different amino acid at position 221, wherein the different amino acid is isoleucine; (l) a different amino acid at position 225, wherein the different amino acid is glutamic acid; (m) a different amino acid at position 227, wherein the different amino acid is serine; (n) a different amino acid at position 231, wherein the different amino acid is isoleucine; (o) a different amino acid at position 233, wherein the different amino acid is proline; (p) a different amino acid at position 235, wherein the different amino acid is serine; (q) a different amino acid at position 236, wherein the different amino acid is lysine; (r) a different amino acid at position 237, wherein the different amino acid is proline; (s) a different amino acid at position 239, wherein the different amino acid is glutamine; (t) a different amino acid at position 240, wherein the different amino acid is glutamic acid; (u) a different amino acid at position 242, wherein the different amino acid is proline; (v) a different amino acid at position 243, wherein the different amino acid is isoleucine; and (w) a different amino acid at position 244, wherein the different amino acid is aspartic acid.

281. The isolated or recombinant polypeptide variant of claim 280, wherein the difference between the amino acid sequence of the variant and the ECD amino acid sequence of the bovine B7-1 further comprises at least one of: (1) a different amino acid at position 246, wherein the different amino acid is leucine; (2) a different amino acid at position 247, wherein the different amino acid is proline; (3) a different amino acid at position 248, wherein the different amino acid is phenylalanine; (4) a different amino acid at position 250, wherein the different amino acid is valine; and (5) a different amino acid at position 253, wherein the different amino acid is proline, wherein each position corresponds to the position in the amino acid sequence of bovine B7-1 of SEQ ID NO:280.

282. The isolated or recombinant polypeptide variant of claim 280, further comprising a signal peptide.

283. The isolated or recombinant polypeptide variant of claim 282, further comprising at least one of a transmembrane domain signal peptide.

284. A nucleic acid comprising a polynucleotide sequence that encodes an isolated or recombinant polypeptide of claim 269, 274, 279, 280, or 281, or a complementary nucleic acid sequence thereof.

285. An isolated or recombinant nucleic acid comprising a polynucleotide sequence that, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of the nucleic acid of claim 269, 274, 279, 280, or 281.

286. The isolated or recombinant polypeptide of claim 1 or 3, wherein the ECD amino acid sequence at least about amino acid residues 35 to 244 of any of SEQ ID NOS:48-68, 174-182, 184-221, 283-285, and 290-293.

287. The isolated or recombinant polypeptide of claim 1 or 3, which comprises a further amino acid sequence corresponding to at least one of

a signal peptide, a transmembrane domain, or a cytoplasmic domain of a co-stimulatory polypeptide.

288. The isolated or recombinant polypeptide of claim 287, wherein the co-stimulatory polypeptide is a B7-1 polypeptide.

289. The isolated or recombinant polypeptide of claim 288, wherein the B7-1 polypeptide is a mammalian B7-1 polypeptide.

290. The isolated or recombinant polypeptide of claim 289, wherein the further amino acid sequence corresponding to the signal peptide sequence comprises at least about amino acid residues 1-34 of a polypeptide selected from the group of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

291. The isolated or recombinant polypeptide of claim 287, wherein the further amino acid sequence corresponding to the transmembrane domain comprises at least about amino acid residues 35-244, 35-243, or 35-242, 35-255, 35-254, or 35-253 of a polypeptide selected from the group of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

292. The isolated or recombinant polypeptide of claim 287, wherein the further amino acid sequence corresponding to the cytoplasmic domain comprises a cytoplasmic domain of a polypeptide selected from the group of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

293. The isolated or recombinant polypeptide of claim 1, which polypeptide comprises an ECD amino acid sequence encoded by an ECD coding nucleotide sequence, the ECD coding nucleotide sequence comprising a nucleotide sequence that, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of the ECD coding nucleotide sequence of a polynucleotide sequence selected from any of SEQ ID NOS:1-21 and 95-142 or the nucleotide coding sequence that encodes the ECD of a polypeptide selected from any of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293.

294. The isolated or recombinant polypeptide of claim 293, further comprising a signal peptide amino acid sequence encoded by a signal peptide coding nucleotide sequence, the signal peptide coding nucleotide sequence selected from the group of: (a) a nucleotide sequence of a polynucleotide sequence selected from any of SEQ ID NOS:1-21 and 95-142, wherein said nucleotide sequence encodes a signal peptide; (b) a nucleotide sequence that encodes the signal peptide of a polypeptide selected from any of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293; and (c) a nucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of a nucleotide sequence (a) or (b).

295. The isolated or recombinant polypeptide of claim 294, further comprising a transmembrane domain (TMD) amino acid sequence encoded by a TMD nucleotide sequence selected from the group of: (a) a nucleotide sequence of a polynucleotide sequence selected from any of SEQ ID NOS:1-21 and 95-142, wherein said nucleotide sequence encodes a TMD polypeptide; (b) a nucleotide sequence that encodes the TMD of a polypeptide selected from any of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293; and (c) a nucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of a nucleotide sequence (a) or (b).

296. The isolated or recombinant polypeptide of claim 295, further comprising a cytoplasmic domain (CD) amino acid sequence encoded by a CD

nucleotide sequence selected from the group of: (a) a nucleotide sequence of a polynucleotide sequence selected from any of SEQ ID NOS:1-21 and 95-142, wherein said nucleotide sequence encodes a CD polypeptide; (b) a nucleotide sequence that encodes the CD of a polypeptide selected from any of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293; and (c) a nucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of a nucleotide sequence (a) or (b).

297. The isolated or recombinant nucleic acid of claim 43, wherein the polynucleotide sequence of (d) comprises encodes a fragment of (a) or (b), wherein the fragment encodes an extracellular domain polypeptide having a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1.

298. The isolated or recombinant polypeptide of claim 96, further comprising a signal peptide amino acid sequence encoded by a signal peptide coding nucleotide sequence, the signal peptide coding nucleotide sequence selected from the group of: (a) a nucleotide sequence comprising a nucleotide fragment of a polynucleotide sequence selected from any of the group of SEQ ID NOS:22-45 and 143-173, wherein said nucleotide fragment encodes a signal peptide; (b) a nucleotide sequence that encodes the signal peptide of a polypeptide selected from any of the group of SEQ ID NOS:69-92, 222-252, and 286-289; and (c) a nucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of a nucleotide sequence (a) or (b).

299. The isolated or recombinant polypeptide of claim 298, further comprising a transmembrane domain (TMD) amino acid sequence encoded by a TMD nucleotide sequence selected from the group of: (a) a nucleotide sequence of a polynucleotide sequence selected from any of the group of SEQ ID NOS:22-45 and 143-173, wherein said nucleotide sequence encodes a TMD polypeptide; (b) a nucleotide sequence that encodes the TMD of a polypeptide selected from any of the group of SEQ ID NOS:69-92, 222-252, and 286-289; and (c) a nucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of a nucleotide sequence (a) or (b).

300. The isolated or recombinant polypeptide of claim 299, further comprising a cytoplasmic domain (CD) amino acid sequence encoded by a CD nucleotide sequence selected from the group of: (a) a nucleotide sequence of a polynucleotide sequence selected from any of the group of SEQ ID NOS:22-45 and 143-173, wherein said nucleotide sequence encodes a CD polypeptide; (b) a nucleotide sequence that encodes the CD of a polypeptide selected from any of the group of SEQ ID NOS:69-92, 222-252, and 286-289, and 290-293; and (c) a nucleotide sequence which, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of a nucleotide sequence (a) or (b).

301. An isolated or recombinant polypeptide comprising an amino acid sequence of at least an extracellular domain, wherein said extracellular domain amino acid sequence has at least about 75% amino acid sequence identity to an extracellular domain amino acid sequence of at least one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, and is not a naturally-occurring extracellular domain amino acid sequence, and wherein said polypeptide has an ability to induce T cell proliferation or T cell activation response that is equal to or greater than that of human B7-1.

302. The isolated or recombinant polypeptide of claim 1 or 301, wherein said polypeptide comprises more than one of the extracellular domain.

303. The isolated or recombinant polypeptide of claim 302, wherein said polypeptide comprises a multimer of the extracellular domain.

304. The isolated or recombinant polypeptide of claim 302, wherein said polypeptide comprises a fusion protein comprising at least one additional amino acid sequence.

305. The isolated or recombinant polypeptide of claim 304, wherein the at least one additional amino acid sequence comprises at least one Ig polypeptide.

306. An isolated or recombinant polypeptide comprising an amino acid sequence of an extracellular domain, wherein said extracellular domain (ECD) amino acid sequence has at least about 75% amino acid sequence identity to an extracellular domain amino acid sequence of at least one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, and is not a naturally-occurring extracellular domain amino acid sequence, and wherein said polypeptide, in the presence of a population of activated T cells, has an ability to induce a T cell proliferation or T cell activation response that is less than that induced by a human B7-1 ECD amino acid sequence in the presence of a population of activated T cells.

307. The isolated or recombinant polypeptide of claim 1 or 306, wherein said polypeptide comprises a soluble ECD monomer.

308. The isolated or recombinant polypeptide of claim 307, wherein said soluble ECD monomer further comprises an Ig polypeptide.

309. A soluble isolated or recombinant multimeric polypeptide comprising at least two polypeptides of claim 1 or 306.

310. The polypeptide of claim 309, wherein each of said at least two polypeptides further comprises at least one additional amino acid sequence which comprises an Ig polypeptide.

311. A nucleic acid comprising a polynucleotide sequence that encodes an isolated or recombinant polypeptide of claim 259, 269, 271, 275, 276, 279, 280, 301, or 306, or a complementary polynucleotide sequence thereof.

312. A vector comprising at least one nucleic acid which comprises a polynucleotide sequence that encodes an isolated or recombinant polypeptide of claim 259, 269, 271, 275, 276, 279, 280, 301, or 306, or a complementary polynucleotide sequence thereof.

313. A composition comprising a nucleic acid of claim 311 and a carrier.

314. A composition comprising a polypeptide of claim 259, 269, 271, 275, 276, 279, 280, 301, or 306 and a carrier.

315. A recombinant nucleic acid molecule comprising a polynucleotide sequence that, but for the degeneracy of the genetic code, hybridizes under at least stringent conditions over substantially the entire length of the nucleic acid of claim 311 or 312.

316. The nucleic acid of claim 43, 44, or 46, wherein the polypeptide has an CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1.

317. The nucleic acid of claim 43, 44, or 46, wherein the polypeptide comprises a soluble polypeptide having an ability in the presence of a population of activated T cells to induce a T cell proliferation response that is less than the T cell proliferation response induced by a soluble human B7-1 polypeptide in the presence of a population of activated T cells.

318. The isolated or recombinant polypeptide of claim 171, wherein said polypeptide has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1, and/or an ability to induce a T-cell proliferation or T-cell activation response about equal to or greater than that of hB7-1.

319. The isolated or recombinant nucleic acid of claim 170, wherein said nucleic acid encodes a polypeptide that has a CTLA-4/CD28 binding affinity ratio about equal to or greater than the CTLA-4/CD28 binding affinity ratio of human B7-1, and/or an ability to induce a T-cell proliferation or T-cell activation response about equal to or less than that of hB7-1.

320. The isolated or recombinant polypeptide of claim 1, 5, 6, or 7, wherein the polypeptide is bound to a cell membrane and has an ability to induce T-cell proliferation or T-cell activation or both.

L26 ANSWER 10 OF 25 USPATFULL on STN
2003:180749 Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer.
Mack, David H., Menlo Park, CA, UNITED STATES
Gish, Kurt C., San Francisco, CA, UNITED STATES
Eos Biotechnology, Inc., South San Francisco, CA (U.S. corporation)
US 2003124579 A1 20030703
APPLICATION: US 2002-235399 A1 20020904 (10)
PRIORITY: US 2002-372246P 20020412 (60)
US 2001-350666P 20011113 (60)
US 2001-317544P 20010905 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of detecting a ovarian cancer-associated transcript in a cell from a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-6.

2. The method of claim 1, wherein the biological sample comprises isolated nucleic acids.

3. The method of claim 2, wherein the nucleic acids are mRNA.

4. The method of claim 2, further comprising the step of amplifying nucleic acids before the step of contacting the biological sample with the polynucleotide.

5. The method of claim 1, wherein the polynucleotide comprises a sequence as shown in Tables 1-6.

6. The method of claim 1, wherein the polynucleotide is immobilized on a solid surface.

7. The method of claim 1, wherein the patient is undergoing a

therapeutic regimen to treat ovarian cancer.

8. The method of claim 1, wherein the patient is suspected of having ovarian cancer.

9. An isolated nucleic acid molecule consisting of a polynucleotide sequence as shown in Tables 1-6.

10. The nucleic acid molecule of claim 9, which is labeled.

11. An expression vector comprising the nucleic acid of claim 9.

12. A host cell comprising the expression vector of claim 11.

13. An isolated polypeptide which is encoded by a nucleic acid molecule having polynucleotide sequence as shown in Tables 1-6.

14. An antibody that specifically binds a polypeptide of claim 13.

15. The antibody of claim 14, further **conjugated** to an effector component.

16. The antibody of claim 15, wherein the effector component is a fluorescent label.

17. The antibody of claim 15, wherein the effector component is a radioisotope or a cytotoxic chemical.

18. The antibody of claim 15, which is an antibody fragment.

19. The antibody of claim 15, which is a humanized antibody

20. A method of detecting a ovarian cancer cell in a biological sample from a patient, the method comprising contacting the biological sample with an antibody of claim 14.

21. The method of claim 20, wherein the antibody is further **conjugated** to an effector component.

22. The method of claim 21, wherein the effector component is a fluorescent label.

23. A method for identifying a compound that modulates a ovarian cancer-associated polypeptide, the method comprising the steps of: (i) contacting the compound with a ovarian cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-6; and (ii) determining the functional effect of the compound upon the polypeptide.

24. A drug screening assay comprising the steps of (i) administering a test compound to a mammal having ovarian cancer or a cell isolated therefrom; (ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-6 in a treated cell or mammal with the level of gene expression of the polynucleotide in a control cell or mammal, wherein a test compound that modulates the level of expression of the polynucleotide is a candidate for the treatment of ovarian cancer.

L26 ANSWER 11 OF 25 USPATFULL on STN

2003:105883 Encapsulation of plasmid DNA (lipogenes.TM.) and therapeutic agents with nuclear localization signal/fusogenic peptide conjugates into targeted liposome complexes.
Boulikas, Teni, Mountain View, CA, UNITED STATES
US 2003072794 A1 20030417
APPLICATION: US 2001-876904 A1 20010608 (9)
PRIORITY: US 2000-210925P 20000609 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for producing micelles with entrapped therapeutic agents, comprising: a) combining an effective amount of a negatively charged therapeutic agent with an effective amount of a cationic lipid in a ratio where about 30% to about 90% the negatively charged atoms are neutralized by positive charges on lipid molecules to form an electrostatic micelle complex in about 20% to about 80% ethanol; and b) combining the micelle complex of step a) with an effective amount of a fusogenic-karyophilic peptide conjugates in a ratio range of about 0.0 to about 0.3, thereby producing micelles with entrapped therapeutic agents.

2. The method of claim 1, wherein the negatively charged therapeutic agent is a therapeutic agent selected from the group consisting of a polynucleotide and a negatively charged drug.

3. The method of claim 2, wherein the polynucleotide is a DNA polynucleotide or an RNA polynucleotide.

4. The method of claim 2, wherein the polynucleotide is a DNA polynucleotide.

5. The method of claim 4, wherein the DNA polynucleotide comprises plasmid DNA.

6. The method of claim 1, further comprising combining an effective amount of an anionic lipid in step a).

7. The method of claim 6, wherein the anionic lipid is dipalmitoyl phosphatidyl glycerol (DDPG) or a derivative thereof.

8. The method of claim 4, further comprising combining an effective amount of a DNA condensing agent selected from the group consisting of spermine, spermidine, polylysine, polyarginine, polyhistidine, polyornithine and magnesium or a divalent metal ion.

9. The method of claim 5, wherein the plasmid DNA comprises a sequence encoding p53, HSV-tk, p21, Bax, Bad, IL-2, IL-12, GM-CSF, angiostatin, endostatin and oncostatin.

10. The method of claim 1, wherein the cationic lipids are selected from the group consisting of 3β-(N--(N',N'-dimethylaminoethane)carbamoyl)cholesterol, dimethyldioctadecyl ammonium bromide (DDAB), N-[1-(2,3-dimyristyloxy)propyl]-N,N-dimethyl-N-(2-hydroxyethyl) ammonium bromide (DMRIE), 1 ,2-dimyristoyl-3-trimethylammonium propane (DMTAP), dioctadecylamidoglycylspermine (DOGS), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), 1,2- dipalmitoyl-3-trimethylammonium propane (DPTAP), 1 ,2-disteroyl-3-trimethylammonium propane (DSTAP).

11. The method of claim 10, wherein the cationic lipids are combined with the fusogenic lipid DOPE in a molar ratio from about 1:1 to about 2:1.

12. The method of claim 11, wherein the cationic lipids are combined with the fusogenic lipid DOPE in a molar ratio of 1:1.

13. The method of claim 1, wherein the fusogenic-karyophilic peptide is an NLS peptide.

14. The method of claim 13, wherein the NLS peptide is a peptide selected from the group consisting of Seq. ID Nos. 20-622.

15. The method of claim 1, wherein the fusogenic-karyophilic peptide **conjugate** is a sole fusogenic peptide.

16. The method of claim 1, wherein the NLS peptide component of the fusogenic-karyophilic peptide **conjugate** is an NLS peptide selected from the group consisting of Seq. ID Nos. 20-622.

17. The method of claim 1, wherein the fusogenic/NLS peptide **conjugates** comprise amino acid sequences selected from the group consisting of (KAWLKAF)3 (SEQ ID NO:1), GLFKAAAKLLKSLWKLLLKA (SEQ ID NO:2), LLLKAFAKLLKSLWKLLLKA (SEQ ID NO:3) as well as all derivatives of the prototype (Hydrophobic3Karyophilic1Hydrophobic2Karyophilic1)2-3 where Hydrophobic is any of the A, I, L, V, P, G, W, F and Karyophilic is any of the K, R, or H, containing a positively-charged residue every 3rd or 4th amino acid, that form alpha helices and direct a net positive charge to the same direction of the helix.

18. The method of claim 1, wherein the fusogenic/NLS peptide **conjugate** comprise an amino acid sequence selected from the group consisting of GLFKAIAGFIKNGWKGMIDGGGYC (SEQ ID NO:4) from influenza virus hemagglutinin HA-2 and YGRKKRRQRRR (SEQ ID NO:5) from TAT of **HIV**.

19. The method of claim 1, wherein the fusogenic/NLS peptide **conjugate** comprise an amino acid sequence selected from the group consisting of MSGTFGGILAGLIGLL(K/R/H)1-6 (SEQ ID NO:6), derived from the N-terminal region of the S protein of duck hepatitis B virus but with the addition of one to six positively-charged lysine, arginine or histidine residues, and combinations of these, GAAIGLAWIPYFGPAA (SEQ ID NO:7) derived from the fusogenic peptide of the Ebola virus transmembrane protein; residues 53-70 (C-terminal helix) of apolipoprotein (apo) All peptide, the 23-residue fusogenic N-terminal peptide of **HIV**-1 transmembrane glycoprotein gp41, the 29-42-residue fragment from Alzheimer's beta-amyloid peptide, the fusion peptide and N-terminal **heptad** repeat of Sendai virus, the 56-68 helical segment of lecithin cholesterol acyltransferase.

20. The method of any of claims 13 to 19, wherein the NLS peptide component in fusogenic/NLS peptide **conjugates** are synthetic peptides containing the above said NLS but further modified by additional K, R, H residues at the central part of the peptide or with P or G at the N- or C-terminus.

21. The method of claim 13, wherein the fusogenic peptide/NLS peptide **conjugates** are linked to each other with a short amino acid stretch representing an endogenous protease cleavage site.

22. The method of claim 1, wherein the structure of the preferred prototype fusogenic/NLS peptide **conjugate** used in this invention is: PKKRRGPSP(L/A/I)12-20 (SEQ ID NO:8) where (L/A/I)12-20 is a stretch of 12-20 hydrophobic amino acids containing A, L, I, Y, W, F and other hydrophobic amino acids.

23. The method of claim 1, wherein the fusogenic/NLS peptide conjugates are added to the mixture of DNA/cationic lipid and are incorporated into micelles.

24. The method of claim 1, further comprising combining an effective amount of an encapsulating lipid solution to step b).

25. The method of claim 24, wherein the encapsulating lipid is a lipid comprising cholesterol (40%), dioleoylphosphatidylethanolamine (DOPE) (20%), palmitoyloleoylphosphatidylcholine (POPC) (12%), hydrogenated soy phosphatidylcholine (HSPC) (10%), distearoylphosphatidylethanolamine (DSPE) (10%), sphingomyelin (SM) (5%), and derivatized vesicle-forming lipid M-PEG-DSPE (3%).

26. The method of claim 24, wherein the encapsulating lipid is a liposome.

27. The method of claim 26, wherein the liposomes comprises vesicle-forming lipids and between about 1 to about 7 mole percent of distearoylphosphatidyl ethanolamine (DSPE) derivatized with an effective amount of polyethyleneglycol.

28. The method of claim 27, wherein the liposomes have a selected average size of about 80 to about 160 nm.

29. The method of claim 27, wherein the polyethyleneglycol has a molecular weight from about 1,000 to about 5,000 daltons.

30. A micelle with an entrapped therapeutic agent produced by the method of claim 1.

31. A liposome encapsulated therapeutic agent produced by the method of claim 24.

32. The method of claim 31, wherein the therapeutic agent further comprises regulation by a liver, spleen or bone marrow regulatory DNA sequence.

33. The method of claim 32, wherein the regulatory DNA sequence is nuclear matrix DNA isolated from liver, spleen or bone marrow cells.

34. A method for delivering a therapeutic agent in vivo, comprising administration of an effective amount of the micelle of claim 30 to a subject.

35. The method of claim 34, wherein the therapeutic agent further comprises regulation by a tumor-specific regulatory DNA sequence.

36. The method of claim 35, wherein the tumor-specific regulatory sequence is nuclear matrix DNA isolated from specific tumor cells.

37. A method for delivering a therapeutic agent in vivo, comprising administration of an effective amount of the liposome encapsulated agent of claim 31 to the subject.

38. The method of claim 34 or 37, wherein the administration is intravenous administration or by injection.

39. A micelle with an entrapped DNA polynucleotide produced by the method of claim 9.

40. A method for reducing tumor size in a subject comprising administration of an effective amount of the micelle of claim 39 to the subject.

41. The method of claim 40, further comprising administration of an effective amount of a second therapeutic agent, wherein the agent is selected from the group consisting of ganciclovir, 5-fluorocytosine, an antisense oligonucleotides a ribozyme, and a triplex-forming oligonucleotide directed against genes that control the cell cycle or signaling pathways.

42. The method of claim 41, further comprising administration of an effective amount of a second therapeutic agent, wherein the second therapeutic agent is selected from the group consisting of adriamycin, angiostatin, azathioprine, bleomycin, busulfane, camptothecin, carboplatin, carmustine, chlorambucile, chlormethamine, chloroquinoxaline sulfonamide, cisplatin, cyclophosphamide, cycloplatam, cytarabine, dacarbazine, dactinomycin, daunorubicin, didox, doxorubicin, endostatin, enloplatin, estramustine, etoposide, extramustinephosphat, flucytosine, fluorodeoxyuridine, fluorouracil, gallium nitrate, hydroxyurea, idoxuridine, interferons, interleukins, leuprolide, lobaplatin, lomustine, mannomustine, mechlorethamine, mechlorethaminoxide, melphalan, mercaptopurine, methotrexate, mithramycin, mitobronitole, mitomycin, mycophenolic acid, nocodazole, oncostatin, oxaliplatin, paclitaxel, pentamustine, platinum-triamine complex, plicamycin, prednisolone, prednisone, procarbazine, protein kinase C inhibitors, puromycine, semustine, signal transduction inhibitors, spiroplatin, streptozotocine, stromelysin inhibitors, taxol, tegafur, telomerase inhibitors, teniposide, thalidomide, thiamiprine, thioguanine, thiotepa, tiamiprine, tretamine, triaziquone, trifosfamide, tyrosine kinase inhibitors, uramustine, vidarabine, vinblastine, vinca alcaloids, vincristine, vindesine, vorozole, zeniplatin, zeniplatin, and zinostatin.

L26 ANSWER 12 OF 25 USPATFULL on STN
2003:57930 Methods for halting unwanted cell growth, such as using ligand-directed nucleic acid delivery vehicles.
Chandler, Lois Ann, Encinitas, CA, UNITED STATES
Sosnowski, Barbara A., Coronado, CA, UNITED STATES
Baird, Andrew, San Diego, CA, UNITED STATES
Pierce, Glenn, Rancho Sante Fe, CA, UNITED STATES
US 2003040496 A1 20030227
APPLICATION: US 2001-861257 A1 20010517 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treating tumors in a patient, comprising administering to the patient a pharmaceutical composition having the formula: receptor-binding internalized ligand--nucleic acid binding domain--cytocide-encoding agent, wherein: the receptor-binding internalized ligand is a polypeptide reactive with a cell surface receptor; the nucleic acid binding domain binds to a nucleic acid, the domain being chemically **conjugated** or fused to the receptor-binding internalized ligand; the cytocide-encoding agent is a nucleic acid molecule encoding a cytocide, the agent being bound to the nucleic acid binding domain; and wherein the receptor-binding internalized ligand--nucleic acid binding domain--cytocide-encoding agent binds to the cell surface receptor and internalizes the cytocide-encoding agent in cells bearing the receptor.

2. A method of treating tumors in a patient, comprising administering to

the patient a pharmaceutical composition having the formula: receptor-binding internalized ligand--nucleic acid binding domain--prodrug-encoding agent, wherein: the receptor-binding internalized ligand is a polypeptide reactive with a cell surface receptor; the nucleic acid binding domain binds to a nucleic acid, the domain being chemically **conjugated** or fused to the receptor-binding internalized ligand; the prodrug-encoding agent is a nucleic acid molecule encoding a prodrug, the agent being bound to the nucleic acid binding domain; and wherein the receptor-binding internalized ligand--nucleic acid binding domain--prodrug-encoding agent binds to the cell surface receptor and internalizes the prodrug-encoding agent in cells bearing the receptor.

3. A method of treating tumors in a patient, comprising administering to the patient a pharmaceutical composition having the formula: receptor-binding internalized ligand--nucleic acid binding domain--cytokine-encoding agent, wherein: the receptor-binding internalized ligand is a polypeptide reactive with a cell surface receptor; the nucleic acid binding domain binds to a nucleic acid, the domain being chemically **conjugated** or fused to the receptor-binding internalized ligand; the cytokine-encoding agent is a nucleic acid molecule encoding a cytokine, the agent being bound to the nucleic acid binding domain; and wherein the receptor-binding internalized ligand--nucleic acid binding domain--cytokine-encoding agent binds to the cell surface receptor and internalizes the cytokine-encoding agent in cells bearing the receptor.

4. The method of any one of claims 1, 2, or 3, wherein the receptor-binding internalized ligand is a polypeptide reactive with an FGF receptor.

5. The method of claim 1 wherein the cytocide-encoding agent encodes a protein that inhibits protein synthesis.

6. The method of claim 5 wherein the protein is a ribosome inactivating protein.

7. The method of claim 6 wherein the ribosome inactivating protein is saporin.

8. The method of claim 6 wherein the ribosome inactivating protein is gelonin.

9. The method of claim 6 wherein the ribosome inactivating protein is Pseudomonas exotoxin.

10. The method of claim 5 wherein the protein inhibits elongation factor 2.

11. The method of claim 10 wherein the protein is diphtheria toxin.

12. The method of claim 2 wherein the prodrug-encoding agent encodes HSV-thymidine kinase or cytosine deaminase.

13. The method of claim 3, wherein the cytokine-encoding agent encodes a cytokine selected from the group consisting of IL-2, IL-10, IL-12 and IFN-γ.

14. The method of claim 3, wherein the cytokine-encoding agent encodes B7 and a cytokine selected from the group consisting of IL-2, IL-10, IL-12 and IFN-γ.

15. The method of any one of claims 1, 2, or 3 wherein the receptor-binding internalized ligand is a polypeptide reactive with the FGF receptor and the nucleic acid binding domain is poly-L-lysine or protamine.

16. The method of any one of claims 1, 2, or 3 wherein the nucleic acid binding domain is selected from the group consisting of helix-turn-helix motif proteins, homeodomain proteins, zinc finger motif proteins, steroid receptor proteins, leucine zipper motif proteins, helix-loop-helix motif proteins, and β-sheet motif proteins.

17. The method of any one of claims 1, 2, or 3 wherein the nucleic acid binding domain is selected from the group consisting of AP-1, Sp-1, rev, GCN4, λcro, λcI, TFIIA, myoD, retinoic acid receptor, glucocosteroid receptor, SV40 large T antigen, and GAL4.

18. The method of any one of claims 1, 2, or 3 wherein the nucleic acid binding domain is a polycation.

19. The method of claim 18 wherein the polycation is selected from the group consisting of poly-L-lysine, poly-D-lysine, protamine, histone and spermine.

20. The method of claim 1 wherein the nucleic acid binding domain binds a DNA molecule that encodes a ribosome inactivating protein.

21. The method of claim 1 wherein the nucleic acid binding domain binds the coding region of saporin DNA.

22. The method of claim 1 wherein the cytocide-encoding agent further comprises a tumor-specific promoter.

23. The method of claim 2 wherein the prodrug-encoding agent further comprises a tumor-specific promoter.

24. The method of either of claims 22 or 23 wherein the tumor-specific promoter is selected from the group consisting of tyrosinase promoter, MAGE promoter, IL-2 receptor promoter, PSA-1 promoter, FGF receptor promoter, erbB2 promoter, erbB3 promoter, erbB4 promoter, MUC-1 promoter, HSP-27 promoter, CEA promoter, EGF receptor promoter, prostate specific antigen-1 promoter, probasin promoter, VEGF receptor promoter, int-1 promoter; int-2 promoter, IL-2 promoter, alpha-fetoprotein promoter, prostatic acid phosphatase promoter, prostate specific membrane antigen promoter, alpha-crystallin promoter and tie-2 promoter.

25. The method of any one of claims 1, 2, or 3, further comprising at least one linker that increases the serum stability, intracellular availability, or condensing ability of the nucleic acid binding domain, the addition of said linker(s) resulting in the formula: receptor-binding internalized ligand--(L)q--nucleic acid binding domain-cytocide encoding agent; receptor-binding internalized ligand--(L)q--nucleic acid binding domain-prodrug encoding agent, or the formula: receptor-binding internalized ligand--(L)q--nucleic acid binding domain-cytokine-encoding agent wherein: L is at least one linker; and q is 1 or more, such that the **conjugate** retains the ability to bind to a cell surface receptor and internalize the cytocide-encoding, prodrug-encoding or cytokine-encoding agent, and wherein the agent is bound to the nucleic acid binding domain.

26. The method of claim 25 wherein the linker increases the flexibility of the **conjugate**.

26. The method of claim 25 wherein the linker is selected from the group consisting of (GlymSerp)n, (SermGlyp)n and (AlaAlaProAla)n in which n is 1 to 6, m is 1 to 6 and p is 1 to 4.

27. The method of claim 26 wherein m is 4, p is 1 and n is 2 to 4.

L26 ANSWER 13 OF 25 USPATFULL on STN
2003:37602 Compositions and methods for generating chimeric heteromultimers.
Wang, Caili, San Francisco, CA, UNITED STATES
Zhong, Pingyu, Mountain View, CA, UNITED STATES
Liu, Shengjiang, Mountain View, CA, UNITED STATES
Luo, Peizhi, Sunnyvale, CA, UNITED STATES
Li, Shengfeng, Belmont, CA, UNITED STATES
Wang, Xinwei, San Jose, CA, UNITED STATES
US 2003027247 A1 20030206
APPLICATION: US 2001-921144 A1 20010801 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A non-single-chain antigen-binding unit comprising: (a) a light (L) chain polypeptide comprising a light (L) chain variable region fused to a first heterodimerization sequence; (b) a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused to a second heterodimerization sequence; wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences; and wherein at least one of the heterodimerization sequences is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures.

2. The non-single-chain antigen-binding unit of claim 1, wherein both of the first and second heterodimerization sequences are essentially incapable of forming homodimers under physiological buffer conditions and at physiological body temperatures.

3. A non-single-chain antigen-binding unit comprising: (a) a light (L) chain polypeptide comprising a light (L) chain variable region fused to a first heterodimerization sequence; (b) a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused to a second heterodimerization sequence; wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences, said first and second heterodimerization sequences comprising heterodimeric receptor sequences that mediate heterodimerization of the receptors.

4. The non-single-chain antigen-binding unit of claim 1 or 3, wherein the first and second heterodimerization sequences form a coiled-coil dimer.

5. The non-single-chain antigen-binding unit of claim 1 or 3, wherein the L and the H chain polypeptides dimerize via non-covalent pairwise affinity of the two heterodimerization sequences.

6. The non-single-chain antigen-binding unit of claim 4, wherein the L chain polypeptide further comprises a flexon that is flanked by the L chain variable region and the first heterodimerization sequence.

7. The non-single-chain antigen-binding unit of claim 4, wherein the H chain polypeptide further comprises a flexon sequence that is flanked by the H chain variable region and the second heterodimerization sequence.

8. The non-single-chain antigen-binding unit of claim 4, wherein both the first and the second heterodimerization sequences contain at least one cysteine residue.

9. The non-single-chain antigen-binding unit of claim 4, wherein the antigen-binding unit is multivalent.

10. The non-single-chain antigen-binding unit of claim 4, wherein the antigen-binding unit is multispecific.

11. The non-single-chain antigen-binding unit of claim 10, wherein the antigen-binding unit is bispecific.

12. The non-single-chain antigen-binding unit of claim 10, wherein the antigen-binding unit is trispecific.

13. The non-single-chain antigen-binding unit of claim 4, wherein the L chain polypeptide comprises sequences derived from a human light chain.

14. The non-single-chain antigen-binding unit of claim 4, wherein the H chain polypeptide comprises sequences derived from a human heavy chain.

15. The non-single-chain antigen-binding unit of claim 4, wherein the antigen-binding unit is **conjugated** to a chemically functional moiety.

16. The non-single-chain antigen-binding unit of claim 15, wherein the moiety is selected from the group consisting of signal peptides, agents that enhance immunologic reactivity, agents that facilitate coupling to a solid support, vaccine carriers, bioresponse modifiers, toxins, detectable labels, paramagnetic labels, and drugs.

17. The non-single-chain antigen-binding unit of claim 4, wherein the first and second heterodimerization sequences are derived from C-terminal sequences of GABAB receptor 1 and GABAB receptor 2, respectively.

18. The non-single-chain antigen-binding unit of claim 4, wherein the first heterodimerization sequence comprising a polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide sequence of comparable length depicted in SEQ ID NO. 2 and wherein the second heterodimerization sequence comprising a polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide sequence of comparable length depicted in SEQ ID NO. 4.

19. The non-single-chain antigen-binding unit of claim 4, wherein the first heterodimerization sequence comprising a polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide sequence of comparable length depicted in SEQ ID NO. 4; and wherein the second heterodimerization sequence comprising a polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide sequence of comparable length depicted in SEQ ID NO. 2.

20. A single-chain antigen-binding unit comprising a light (L) chain variable region and a heavy (H) chain variable region connected by a first and a second heterodimerization sequence spanning the distance between the C-terminus of one of the region to the N-terminus of the other region, wherein the two regions form an intra-molecular dimer via pairwise affinity of the first and second heterodimerization sequences; and wherein at least one of the heterodimerization sequences is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures.

21. The single-chain antigen-binding unit of claim 20, wherein both of the first and second heterodimerization sequences are essentially incapable of forming homodimers under physiological buffer conditions and at physiological body temperatures.

22. A single-chain antigen-binding unit comprising a light (L) chain variable region and a heavy (H) chain variable region connected by a first and a second heterodimerization sequence spanning the distance between the C-terminus of one of the region to the N-terminus of the other region, wherein the two regions form an intra-molecular dimer via pairwise affinity of the first and second heterodimerization sequences, said first and second heterodimerization sequences comprising heterodimeric receptor sequences that mediate heterodimerization of the receptors.

23. The single-chain antigen-binding unit of claim 20 or 22, wherein the first and second heterodimerization sequences form a coiled-coil dimer.

24. The single-chain antigen-binding unit of claim 20 or 22, wherein the first and second heterodimerization sequences dimerize via non-covalent pairwise affinity.

25. The single-chain antigen-binding unit of claim 23, wherein the antigen-binding unit is **conjugated** to a chemically functional moiety.

26. The single-chain antigen-binding unit of claim 23, wherein the L chain variable region comprises sequences derived from a human light chain.

27. The single-chain antigen-binding unit of claim 23, wherein the H chain variable region comprises sequences derived from a human heavy chain.

28. The single-chain antigen-binding unit of claim 23, wherein the first and second heterodimerization sequences are derived from C-terminal sequences of GABAB receptor 1 and GABAB receptor 2, respectively.

29. The single-chain antigen-binding unit of claim 23, wherein the first heterodimerization sequence comprising a polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide sequence of comparable length depicted in SEQ ID NO. 2; and wherein the second heterodimerization sequence comprising a polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide sequence of comparable length depicted in SEQ ID NO. 4.

30. The single-chain antigen-binding unit of claim 23, wherein the first heterodimerization sequence comprising a polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide sequence of comparable length depicted in SEQ ID NO. 4; and wherein the second heterodimerization sequence comprising a polypeptide of at least 30 amino acid residues that is essentially identical to a linear peptide sequence of comparable length depicted in SEQ ID NO. 2.

31. A recombinant polynucleotide comprising a coding sequence that encodes L chain polypeptide of claim 1.

32. A recombinant polynucleotide comprising a coding sequence that encodes the H chain polypeptide of claim 1.

33. A recombinant polynucleotide comprising a first coding sequence that encodes the L chain polypeptide of claim 1, and a second coding sequence

that encodes the H chain of polypeptide of claim 1.

34. A recombinant polynucleotide comprising a coding sequence that encodes the L chain polypeptide of claim 3.

35. A recombinant polynucleotide comprising a coding sequence that encodes the H chain polypeptide of claim 3.

36. A recombinant polynucleotide comprising a first coding sequence that encodes the L chain polypeptide of claim 3, and a second coding sequence that encodes the H chain of polypeptide of claim 3.

37. A recombinant polynucleotide comprising a coding sequence that encodes the single-chain antigen-binding unit of claim 20.

38. A recombinant polynucleotide comprising a coding sequence that encodes the single-chain antigen-binding unit of claim 22.

39. A vector comprising the recombinant polynucleotide of any one of claims 31-38.

40. The vector of claim 39, wherein the vector is an expression vector.

41. The vector of claim 39, wherein the vector is a phage display vector.

42. A selectable library of expression vectors encoding a repertoire of antigen binding units, comprising more than one vector of claim 39.

43. The selectable library of claim 39, wherein the vector is a phage display vector.

44. A host cell comprising the recombinant polynucleotides of any one of claims 31-38.

45. The host cell of claim 44, wherein the recombinant polynucleotide encoding the L chain polypeptide and the polynucleotide encoding the H chain polypeptide, are present in a single vector.

46. The host cell of claim 44, wherein the recombinant polynucleotide encoding the L chain polypeptide and the polynucleotide encoding the H chain polypeptide, are present in separate vectors.

47. The host cell of claim 44, wherein the host cell is a eukaryotic cell.

48. The host cell of claim 44, wherein the host cell is a prokaryotic cell.

49. A method of producing a non-single-chain antigen-binding unit, comprising: (a) expressing in a host cell a first recombinant polynucleotide encoding a light (L) chain polypeptide comprising a light (L) chain variable region fused to a first heterodimerization sequence, and a second recombinant polynucleotide encoding a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused to a second heterodimerization sequence; wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences; and wherein at least one of the heterodimerization sequences is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures; and optionally (b) isolating the antigen-binding unit expressed in the host cell.

50. A method of claim 49, wherein both of the first and second heterodimerization sequences are essentially incapable of forming homodimers under physiological buffer conditions and at physiological body temperatures.

51. A method of producing a non-single-chain antigen-binding unit, comprising: (a) expressing in a host cell a first recombinant polynucleotide encoding a light (L) chain polypeptide comprising a light (L) chain variable region fused to a first heterodimerization sequence, and a second recombinant polynucleotide encoding a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused to a second heterodimerization sequence; wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences, said first and second heterodimerization sequences comprising heterodimeric receptor sequences that mediate heterodimerization of the receptors; and optionally (b) isolating the antigen-binding unit expressed in the host cell.

52. The method of claim 49 or 51, wherein the non-single-chain antigen-binding expressed in step (a) is displayed on surface of the host cell.

53. The method of claim 49 or 51, wherein the non-single-chain antigen-binding expressed in step (a) is displayed on a phage particle.

54. The method of claim 49 or 51, wherein the host cell is a eukaryotic cell.

55. The method of claim 49 or 51, wherein the host cell is a prokaryotic cell.

56. The method of claim 49 or 51, wherein the first and second heterodimerization sequences form a coiled-coil dimer.

57. The method of claim 49 or 51, wherein the L chain and the H chain polypeptides dimerize via non-covalent pairwise affinity.

58. The method of claim 56, wherein the L chain polypeptide further comprises a flexon that is flanked by the L chain variable region and the first heterodimerization sequence.

59. The method of claim 56, wherein the H chain polypeptide further comprises a flexon sequence that is flanked by the H chain variable region and the second heterodimerization sequence.

60. The method of claim 56, wherein both the first and the second heterodimerization sequences contain at least one cysteine residue.

61. The method of claim 56, wherein the non-single-chain antigen-binding unit is multivalent.

62. The method of claim 56, wherein the non-single-chain antigen-binding unit is multispecific.

63. The method of claim 62, wherein the non-single-chain antigen-binding unit is bispecific.

64. The method of claim 62, wherein the non-single-chain antigen-binding unit is trispecific.

65. The method of claim 56, wherein the L chain polypeptide comprises

sequences derived from a human light chain.

66. The method of claim 56, wherein the H chain polypeptide comprises sequences derived from a human heavy chain.

67. A method of producing a non-single-chain antigen-binding unit, comprising: (a) preparing a first recombinant polynucleotide encoding a light (L) chain polypeptide comprising a light (L) chain variable region fused to a first heterodimerization sequence, and a second recombinant polynucleotide encoding a heavy (H) chain polypeptide comprising a heavy (H) chain variable region fused to a second heterodimerization sequence; wherein the L chain and the H chain polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences; and wherein at least one of the heterodimerization sequences is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures; and (b) allowing the first and second polypeptides to dimerize via pairwise affinity of the first and second heterodimerization sequences.

68. The method of claim 67, wherein step (b) comprises dimerizing the first and the second polypeptides in vitro.

69. A method of producing a single-chain antigen-binding unit, comprising: (a) expressing in a host cell a polynucleotide comprising a coding sequence that encodes the single-chain antigen-binding unit of claim 20 or 22; and optionally (b) isolating the single-chain antigen-binding unit expressed in the host cell.

70. The method of claim 69, wherein the polynucleotide is contained in a phage display vector.

71. A method of displaying a chimeric heteromultimer comprising at least two polypeptides on a surface of a host cell, the method comprising: expressing in the host cell (a) a first recombinant polynucleotide encoding a first polypeptide fused to a first heterodimerization sequence and a surface presenting sequence; (b) a second recombinant polynucleotide encoding a second polypeptide fused to a second heterodimerization sequence; wherein the first and second polypeptides dimerize via pairwise affinity of the first and second heterodimerization sequences; wherein at least one of the heterodimerization sequences is incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures.

72. The method of claim 71, wherein both of the first and second heterodimerization sequences are essentially incapable of forming homodimers under physiological buffer conditions and at physiological body temperatures.

73. The method of claim 71, wherein the first and second heterodimerization sequences form a coiled-coil dimer.

74. The method of claim 71, wherein the first and second polynucleotides are expressed by a single phage display vector.

75. The method of claim 71, wherein the first and second polynucleotides are expressed by separate phage display vectors.

76. The method of claim 71, wherein the host cell is a prokaryotic cell.

77. The method of claim 71, wherein the host cell is a eukaryotic cell.

78. The method of claim 71, wherein the chimeric heteromultimer is a non-single-chain antigen-binding unit.

79. A chimeric heteromultimer displayed on the surface of the host cell according to the method of claim 71.

80. A method of identifying a non-single-chain antigen-binding unit that is immunoreactive with a desired antigen, comprising: (a) preparing a genetically diverse repertoire of antigen-binding units, wherein the repertoire comprises more than one antigen-binding unit of claim 1 or 3; (b) contacting the repertoire of antigen binding units with the desired antigen; (c) detecting a specific binding between antigen binding units and the antigen, thereby identifying the antigen-binding unit that is immunoreactive with the desired antigen.

81. The method of claim 80, wherein the repertoire of antigen-binding units are prepared by expressing a library of vectors encoding a plurality of the antigen-binding units.

82. The method of claim 80, wherein the library of vectors comprises a plurality of phage vectors.

83. A method of identifying a single-chain antigen-binding unit that is immunoreactive with a desired antigen, comprising: (a) preparing a genetically diverse repertoire of single-chain antigen-binding units, wherein the repertoire comprises at least one antigen-binding unit of claim 20 or 22; (b) contacting the repertoire of antigen-binding units with the desired antigen; detecting a specific binding between antigen-binding units and the antigen, thereby identifying the single-chain antigen-binding unit that is immunoreactive with the desired antigen.

84. The method of claim 83, wherein the repertoire of antigen-binding units are prepared by expressing a library of vectors encoding a plurality of the antigen-binding units.

85. The method of claim 83, wherein the library of vectors comprises a plurality of phage vectors.

86. A kit comprising a vector of claim 39 in suitable packaging.

L26 ANSWER 14 OF 25 USPATFULL on STN
2003:26157 Therapy for human cancers using cisplatin and other drugs or genes encapsulated into liposomes.
Boulikas, Teni, 249 Matadero Ave., Palo Alto, CA, United States 94306
US 6511676 B1 20030128
APPLICATION: US 1999-434345 19991105 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for producing cisplatin micelles, comprising: a) combining a suitable buffer solution, cisplatin with an effective amount of at least a 30% ethanol solution to form a cisplatin/ethanol solution; and b) combining the solution with a negatively charged phosphatidyl glycerol lipid derivative wherein the molar ratio between cisplatin and the lipid derivative is 1:1 to 1:2, thereby producing a cisplatin mixture in its aqua form in micelles.

2. A method of producing cisplatin micelles, comprising: a) combining a suitable buffer solution, cisplatin with an effective amount of at least 30% ethanol solution to form a cisplatin/ethanol solution; and b)

combining the cisplatin/ethanol solution with a negatively charged phosphatidyl glycerol lipid derivative wherein the molar ratio between cisplatin and the lipid derivative is 1:1 to 1:2, thereby producing a cisplatin mixture in its aqua form in micelles.

3. The method of claim 1 or 2, wherein the phosphatidyl glycerol lipid derivative is selected from the group consisting of dipalmitoyl phosphatidyl glycerol (DPPG), dimyristoyl phosphatidyl glycerol (DMPG), dicaproyl phosphatidyl glycerol (DCPG), distearoyl phosphatidyl glycerol (DSPG) and dioleyl phosphatidyl glycerol (DOPG).

4. The method of claim 1 or 2, wherein the molar ratio is 1:1.

5. The method of claim 1 or 2, further comprising combining an effective amount of a free fusogenic peptide, a fusogenic peptide-lipid **conjugate** or a fusogenic peptide--**PEG**-HSPC **conjugate** to the mixture of step a) where the fusogenic peptide is derivatized with a stretch of 1-6 negatively-charged amino acids at the N or C-terminus and thus, able to bind electrostatically to the cisplatin mixture in its aqua form.

6. The method of claim 5, wherein the free fusogenic peptide or fusogenic peptide lipid **conjugate** comprises DOPE or DOPE/cationic lipid.

7. The cisplatin micelle obtained by the method of claim 5.

8. The cisplatin micelle obtained by the method of claim 1 or 2.

9. A method for penetrating the cell membrane of a tumor cell in a subject comprising administering an effective amount of the cisplatin micelle obtainable by the method of claim 8.

10. A method for encapsulating cisplatin micelles, comprising mixing an effective amount of a vesicle-fonming lipid with the cisplatin micelles of claim 1 or 2.

11. The encapsulated cisplatin lipid micelle obtainable by the method of claim 10.

12. A method for obtaining a cisplatin/lipid complex capable of evading macrophages and cells of the immune system when administered to a subject, the method comprising mixing an effective amount of the cisplatin micelles of claim 11 with an effective amount of lipid selected from the group consisting of **PEG**-DSPE, **PEG**-DSPC and hyaluronic acid--DSPE.

13. An encapsulated cisplatin/lipid complex obtainable by the method of claim 12.

14. A method for delivering cisplatin to a cell comprising contacting the cell with the encapsulated cisplatin/lipid complex of claim 13.

15. A method for inhibiting the growth of a tumor in a subject, comprising administering to the subject an effective amount of the encapsulated cisplatin/lipid complex of claim 13.

16. A composition comprising the encapsulated cisplatin micelle of claim 11 and encapsulated oligonucleotides, ribozymes, triplex, PNA.

17. A composition comprising the encapsulated cisplatin micelle of claim 11 and a drug selected from the group consisting of doxorubicin, fluorodeoxyuridine, bleomycin, adriamycin, vinblastin, prednisone,

vincristine, taxol.

18. The method of claim 10, wherein the lipid is selected from the group consisting of pre-made neutral liposomes comprising 10%-60% cholesterol, 40-90% hydrogenated soy phosphatidylcholine (HSPC), 1-7% polyethyleucglycol (PEG)-HSPC and PEG-DSPE.

19. An encapsulated cisplatin lipid micelle obtainable by the method of claim 18.

20. A method for delivering cisplatin to a cell comprising contacting the cell with the encapsulated cisplatin lipid micelle of claim 19.

21. A method for inhibiting the growth of a tumor in a subject, comprising administering to the subject an effective amount of the encapsulated cisplatin lipid micelle of claim 19.

22. A method for targeting solid tumors and metastases in a subject comprising intravenous administration of an effective amount of the encapsulated cisplatin micelle of claim 19 or the cisplatin/lipid complex of claim 13.

23. The method of claim 10, wherein the lipid comprises 10-60% cholesterol.

24. The method of claim 10, wherein the vesicle-forming lipid is in solution or powder form.

25. The method of claim 1 or 2, further comprising removal of the ethanol from the cisplatin micelles.

26. The method of claim 25, wherein removal of the ethanol is by dialysis of the cisplatin micelles through permeable membranes to remove the ethanol.

L26 ANSWER 15 OF 25 USPATFULL on STN
2003:6894 Compositions containing nucleic acids and ligands for therapeutic treatment.
Baird, J. Andrew, San Diego, CA, United States
Chandler, Lois Ann, Encinitas, CA, United States
Sosnowski, Barbara A., Coronado, CA, United States
Selective Genetics, Inc., San Diego, CA, United States (U.S. corporation)
US 6503886 B1 20030107
APPLICATION: US 1999-449249 19991124 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A gene delivery composition having the formula: polypeptide that binds to a fibroblast growth factor (FGF) receptor-nucleic acid molecule, wherein: the nucleic acid molecule being chemically **conjugated** or fused to the polypeptide that binds to an FGF receptor; and wherein the gene delivery composition binds to an FGF receptor and is internalized specifically in cells bearing the FGF receptor.

2. The composition of claim 1 wherein the nucleic acid molecule is a agent.

3. The composition of claim 2 wherein the cytocide-encoding agent encodes a ribosome inactivating protein.

4. The composition of claim 3 wherein the ribosome inactivating protein

is saporin.

5. The composition of claim 2 wherein the cytocide-encoding agent encodes its elongation factor 2.

6. The composition of claim 3 wherein the ribosome inactivating protein is gelonin.

7. The composition of claim 5 wherein the protein is diphtheria toxin.

8. The composition of claim 1 wherein the nucleic acid molecule is a prodrug-encoding agent.

9. The composition of claim 8, wherein the prodrug-encoding agent encodes HSV-thymidine kinase or cytosine deaminase.

10. The composition of claim 5 wherein the composition further comprises a polycation.

11. The composition of claim 10 wherein the polycation is selected from the group consisting of poly-L-lysine, protamine, histone and spermine.

12. The composition of claim 1 wherein the nucleic acid molecule encodes a ribozyme or an antisense molecule.

13. A method of delivering a nucleic acid molecule to a cell, comprising contacting a cell with the composition according to any one of claims 1-10 wherein the nucleic acid molecule is internalized in the cell.

14. The composition of either of claims 5, 2, 8, or 12 wherein the polypeptide that binds to an FGF receptor is selected from the group consisting of an FGF-1 polypeptide, an FGF-2 polypeptide, an FGF-3 polypeptide, an FGF-4 polypeptide, an FGF-5 polypeptide, an FGF-6 polypeptide, an FGF-7 polypeptide, an FGF-8 polypeptide and an FGF-9 polypeptide.

15. The composition of claim 14 wherein the polypeptide that binds to an FGF receptor is an FGF-2 polypeptide.

16. The composition of claim 15 wherein FGF-2 of SEQ ID NO:11 has a serine residue at position 96.

17. The composition of claim 1 wherein the nucleic acid molecule further comprises a tissue-specific promoter operably linked thereto.

18. The composition of claim 17 wherein the tissue-specific promoter is selected from the group consisting of alpha-crystalline promoter, tyrosinase promoter, α-fetoprotein promoter, prostate specific antigen promoter, CEA promoter, α-actin promoter, VEGF receptor promoter, erbB-2 promoter, C-myc promoter, cyclin D promoter, FGF receptor promoter gamma-crystalline promoter, tek promoter, tie promoter, urokinase receptor promoter, E-selectin promoter, P-selectin promoter, VCAM-1 promoter, endoglin promoter, endosialin promoter, alphav integrin promoter, β3 integrin promoter, endothelin-1 promoter, ICAM-3 promoter, B9 promoter, von Willebrand Factor promoter, CD-44 promoter, CD40 promoter, vascular endothelial cadherin promoter, notch 4 promoter and high molecular weight melanoma-associated antigen promoter.

19. The composition of claim 14 wherein the polypeptide that binds to an FGF receptor is an FGF-7 polypeptide.

20. The composition of either of claims 1, 2, 8, or 12 further comprising between one to six linkers that are selected from the group consisting of a cleavable linker, a linker that provides a sorting signal, and a linker that reduces steric hindrance, the addition of said one to six linkers resulting in the following formula: polypeptide that binds to an FGF receptor--L--ucleic acid molecule, wherein L is one to six linkers; and wherein the **conjugate** retains the ability to bind to an FGF receptor and internalize the nucleic acid molecule.

21. The composition of claim 20 wherein the linker is selected from the group consisting of a GlySer linker, a SerGly linker, or an AlaAlaProAla (SEQ ID NO: 51) linker.

22. The composition of claim 21 wherein the linker is encoded by a sequence selected from the group consisting of SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50.

23. The composition of claim 20 wherein the linker is a disulfide bond.

24. The composition of claim 20 wherein the polypeptide that binds to an FGF receptor is selected from the group consisting of an FGF-1 polypeptide, an FGF-2 polypeptide, an FGF-3 polypeptide, an FGF-4 polypeptide, an FGF-5 polypeptide, an FGF-6 polypeptide, an FGF-7 polypeptide, an FGF-8 polypeptide and an FGF-9 polypeptide.

25. The composition of claim 20 wherein the polypeptide that binds to an FGF receptor is an FGF-2 polypeptide.

26. The composition of claim 25 wherein FGF-2 of SEQ ID NO:11 has a serine residue at position 96.

27. The composition of claim 20 wherein the polypeptide that binds to an FGF receptor is an FGF-7 polypeptide.

28. The composition of claim 27 wherein the protease is selected from the group consisting of cathepsin B, cathepsin D and trypsin.

29. The composition of claim 20 wherein the cleavable linker is cleavable by a protease.

L26 ANSWER 16 OF 25 USPATFULL on STN
2002:300795 COMPOSITIONS AND METHODS FOR DELIVERY OF AGENTS FOR NEURONAL REGENERATION AND SURVIVAL.
BAIRD, ANDREW, UNITED STATES
US 2002168338 A1 20021114
APPLICATION: US 1998-178286 A1 19981023 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A device for promoting neuronal regeneration, comprising: a gene activated matrix comprising a biocompatible matrix and at least one neuronal therapeutic encoding agent having an operably linked promoter.

2. A device for promoting neuronal survival, comprising: a gene activated matrix comprising a biocompatible matrix and at least one neuronal therapeutic encoding agent having an operably linked promoter.

3. The device of either claim 1 or claim 2 wherein the promoter is an inducible promoter.

4. The device of either claim 1 or claim 2 wherein the promoter is a

tissue specific promoter.

5. The device of either claim 1 or claim 2 wherein the promoter is selected from the group consisting of GAP43 promoter, GFAP promoter, neuron specific enolase promoter, FGF-receptor promoter, elastase I gene control region, immunoglobulin gene control region, alpha-1-antitrypsin gene control region, beta-globin gene control region, myelin basic protein gene control region, myosin light chain 2 gene control region, RSV promoter, vaccinia virus 7.5K promoter, SV40 promoter, HSV promoter, MLP adenovirus promoter, MMTV LTR promoter, CMV promoter, metallothionein promoter, a promoter having at least one cAMP response element, tie promoter, VCAM-1 promoter, alpha V-beta 3 integrin promoters, ICAM-3 promoter, CD44 promoter, CD40 promoter, notch 4 promoter, and an event type-specific promoter.

6. The device of either claim 1 or claim 2 wherein the promoter is a neuronal cell specific promoter.

7. The device of claim 6 wherein the promoter is selected from the group consisting of GAP43 promoter, FGF receptor promoter and neuron specific enolase promoter.

8. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent encodes a neurotrophic factor.

9. The device of claim 8 wherein the neurotrophic factor is a member of the neurotrophin family.

10. The device of claim 8 wherein the neurotrophic factor is a member of the FGF family.

11. The device of claim 8 wherein the neurotrophic factor is selected from the group consisting of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), cardiotrophin-1 (CT-1), choline acetyltransferase development factor (CDF), ciliary neurotrophic factor (CNTF), oncostatin M (OSM); fibroblast growth factor-1 (FGF-1), FGF-2, FGF-5, glial cell-line-derived neurotrophic factor (GDNF), insulin, insulin-like growth factor-1 (IGF-1), IGF-2, interleukin-6 (IL-6), leukemia inhibitor factor (LIF), neurite promoting factor (NPF), neurotrophin-3 (NT-3), NT-4, platelet-derived growth factor (PDGF), protease nexin-1 (PN-1), S-100, transforming growth factor-β (TGF-β), and vasoactive intestinal peptide (VIP).

12. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent encodes an inhibitor of an antagonist of axonal generation or regeneration.

13. The device of claim 12 wherein the inhibitor of an antagonist of axonal generation or regeneration is an inhibitor of TGF-beta.

14. The device of claim 13 wherein the inhibitor of TGF-beta is selected from the group consisting of decorin, a TGF-beta inhibitory chemokine, an anti-TGF-beta antibody, an antisense TGF-beta oligonucleotide, a TGF-beta gene specific ribozyme and a mutated TGF-beta.

15. The device of claim 14 wherein the TGF-beta inhibitory chemokine is an ELR containing member of the CXC chemokine family.

16. The device of claim 15 wherein the ELR containing member of the CXC chemokine family is selected from the group consisting of interleukin-8, ENA-78, GROα, GROβ and GROγ.

17. The device of claim 13 wherein the inhibitor of TGF-beta is decorin.

18. The device of claim 13 wherein the inhibitor of TGF-beta is an anti-TGF-beta antibody.

19. The device of claim 13 wherein the inhibitor of TGF-beta is a mutated TGF-beta.

20. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent is non-covalently associated with the gene activated matrix.

21. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent is adsorbed to the gene activated matrix.

22. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent is absorbed in the gene activated matrix.

23. The device of either claim 1 or claim 2 wherein the neuronal therapeutic encoding agent is capable of inducing neuronal axonal generation or regeneration.

24. A device for promoting neuronal regeneration, comprising: a gene activated matrix; at least one support cell; and at least one neuronal therapeutic encoding agent having an operably linked promoter.

25. A device for promoting neuronal survival, comprising: a gene activated matrix; at least one support cell; and at least one neuronal therapeutic encoding agent having an operably linked promoter.

26. The device of either claim 24 or claim 25 wherein the support cell is a Schwann cell.

27. The device of either claim 24 or claim 25 wherein the support cell is an oligodendrocyte.

28. The device of either claim 24 or claim 25 wherein the support cell is an astrocyte.

29. The device of either claim 24 or claim 25 wherein the support cell is a microglial cell.

30. The device of either claim 24 or claim 25 wherein the support cell is a fibroblast.

31. The device of either claim 24 or claim 25 wherein the support cell is a macrophage.

32. The device of either claim 24 or claim 25 wherein the support cell is an inflammatory cell selected from the group consisting of a macrophage, a neutrophil, a monocyte, a granulocyte and a lymphocyte.

33. The device of any one of claims 1, 2, 24 or 25 wherein the neuronal therapeutic encoding agent is capable of maintaining axonal generation or regeneration.

34. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is an implant for a neuronal injury site.

35. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is formed upon administration.

36. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is administered to a neuronal injury site.

37. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is a composition selected from the group consisting of a solution, a paste, a suspension, a powder, a semisolid, an emulsion and a gel.

38. The device of any one of claims 1, 2, 24 or 25 wherein the gene activated matrix is a paste.

39. The device of any one of claims 1, 2, 24 or 25 wherein the neuronal therapeutic encoding agent is selected from the group consisting of a nucleic acid molecule, a vector, an antisense nucleic acid molecule and a ribozyme.

40. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is complexed with the neuronal therapeutic encoding agent and is capable of binding a neuronal cell surface receptor.

41. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is **conjugated** to the neuronal therapeutic encoding agent and is capable of binding a neuronal cell surface receptor.

42. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is complexed with the neuronal therapeutic encoding agent and is capable of binding a repair cell surface receptor.

43. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is **conjugated** to the neuronal therapeutic encoding agent and is capable of binding a repair cell surface receptor.

44. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is complexed with the neuronal therapeutic encoding agent and is capable of binding extracellular matrix.

45. The device of any one of claims 1, 2, 24 or 25, further comprising a targeting agent, wherein said targeting agent is **conjugated** to the neuronal therapeutic encoding agent and is capable of binding extracellular matrix.

46. The device of any one of claims 1, 2, 24 or 25, further comprising a nucleic acid binding domain, wherein said nucleic acid binding domain binds to a nucleic acid sequence that forms a portion of the neuronal therapeutic encoding agent.

47. The device of any one of claims 1, 2, 24 or 25, further comprising at least one linker that is selected from the group consisting of a cleavable linker, a linker that provides an intracellular protein sorting peptide sequence, a linker that reduces steric hindrance, a linker that provides a nuclear translocation signal and a linker that possesses a nucleic acid condensing ability.

48. The device of any one of claims 1, 2, 24 or 25 wherein the device contains sub-physiologic amounts of a neuronal therapeutic agent.

49. The device of any one of claims 1, 2, 24 or 25 wherein the device

contains physiologic amounts of a neuronal therapeutic agent.

50. A device according to any one of claims 1, 2, 24 or 25, further comprising a conduit having a lumen.

51. The device of claim 50 wherein the conduit comprises the gene activated matrix.

52. The device of claim 50 wherein the lumen contains the gene activated matrix.

53. The device of claim 50 wherein the conduit comprises a bioabsorbable material.

54. The device of claim 53 wherein the bioabsorbable material comprises material selected from the group consisting of gene activated matrix, type I collagen, laminin, polyglycolic acid, glycolide trimethylene carbonate (GTMC), poly (L-lactide-co-6-caprolactone), glycoproteins, proteoglycans, heparan sulfate proteoglycan, nidogen, glycosaminoglycans, fibronectin, epidermal growth factor, fibroblast growth factor, nerve growth factor, cytokines, and DNA encoding growth factors and cytokines.

55. The device of claim 50 wherein the conduit comprises a non-bioabsorbable material.

56. The device of claim 55 wherein the non-bioabsorbable material is selected from the group consisting of polyamide, polyimide, polyurethane, segmented polyurethane, polycarbonate, and silicone.

57. The device of claim 55 wherein the non-bioabsorbable material comprises an etched microporous synthetic polymer surface.

58. The device of claim 50 wherein the conduit is tubular.

59. A method for transferring a neuronal therapeutic encoding agent into a neuronal cell, comprising: contacting a neuronal cell with the device of any one of claims 1-58 to effectively transfer the neuronal therapeutic encoding agent into the neuronal cell.

60. The method of claim 59 wherein transfer of the neuronal therapeutic encoding agent comprises retrograde axonal transport of the neuronal therapeutic encoding agent.

61. The method of claim 59, further comprising expression of the neuronal therapeutic encoding agent at a neuronal cellular site distinct from a site of contact between the device and the neuronal cell.

62. The method of claim 59 wherein the device is contacted with a neuronal cell at a neuronal injury site.

63. The method of claim 59 wherein the device is contacted with a neuronal cell in a manner such that axonal generation or regeneration occurs.

64. The method of claim 63 wherein axonal regeneration occurs without axonal entrapment.

65. The method of claim 59 wherein the device is contacted with a neuronal cell in a manner that promotes neuronal survival.

66. The method of claim 65 wherein neuronal survival is promoted without

axonal entrapment.

67. The method of any one of claims 62, 63, 64, 65 or 66 wherein a neural connection is established or reestablished.

68. A method for transferring a neuronal therapeutic encoding agent into a repair cell, comprising: contacting a repair cell with the device of any one of claims 1-58 to effectively transfer the neuronal therapeutic encoding agent into the repair cell.

69. The method of claim 68 wherein the device is contacted with a repair cell at a neuronal injury site.

70. The method of claim 68 wherein the device is contacted with a repair cell in a manner such that axonal generation or regeneration occurs.

71. The method of claim 70 wherein axonal generation or regeneration occurs without axonal entrapment.

72. The method of claim 68 wherein the device is contacted with a repair cell in a manner that promotes neuronal survival.

73. The method of claim 72 wherein neuronal survival is promoted without axonal entrapment.

74. The method of any one of claims 69, 70, 71, 72 or 73 wherein a neural connection is established or reestablished.

75. The method of either claim 59 or claim 68 wherein the device contains sub-physiologic amounts of a neuronal therapeutic agent.

76. The method of either claim 59 or claim 68 wherein the device contains physiologic amounts of a neuronal therapeutic agent.

77. A method of preparing a gene activated matrix for promoting neuronal regeneration and survival, comprising contacting a neuronal therapeutic encoding agent with a biocompatible matrix such that the neuronal therapeutic encoding agent associates non-covalently with the matrix.

78. The method of claim 77 wherein the neuronal therapeutic encoding agent is adsorbed to the gene activated matrix.

79. The method of claim 77 wherein the neuronal therapeutic encoding agent is absorbed in the gene activated matrix.

80. The method of claim 77 wherein the neuronal therapeutic encoding agent is selected from the group consisting of a nucleic acid molecule, a vector, an antisense molecule and a ribozyme.

L26 ANSWER 17 OF 25 USPATFULL on STN
2002:160573 Methods for generating polynucleotides having desired characteristics by iterative selection and recombination.
Stemmer, Willem P. C., Los Gatos, CA, United States
Cramieri, Andreas M., Mountain View, CA, United States
Maxygen, Inc., Redwood City, CA, United States (U.S. corporation)
US 6413774 B1 20020702
APPLICATION: US 1999-240734 19990129 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of producing a recombinant nucleic acid with a desired

property from at least two nucleic acids, the method comprising: (a) providing single-stranded segments of the at least two nucleic acids; (b) hybridizing the single-stranded segments to produce partially or fully annealed nucleic acid strands and elongating the partially or fully annealed nucleic acid strands to produce recombinant nucleic acids; (c) denaturing the recombinant nucleic acids to form recombinant single-stranded nucleic acids; (d) hybridizing the single-stranded recombinant nucleic acids of step (c) to produce additional partially or fully annealed nucleic acid strands; (e) elongating the partially or fully-annealed nucleic acid strands of step (d) to produce transferrable recombinant nucleic acids; (f) transferring the transferrable recombinant nucleic acids into one or more cells; and, (g) recombining the transferrable recombinant nucleic acids in the one or more cells to produce additional recombinant nucleic acids.

2. The method of claim 1, further comprising selecting or screening the additional recombinant nucleic acids for one or more trait or property.

3. A method of recombining one or more nucleic acids, the method comprising: (a.) producing a plurality of transferrable nucleic acids in vitro; (b.) transferring the transferrable nucleic acids into one or more cells; (c.) recombining the transferrable nucleic acids with each other or with one or more first additional nucleic acids in the cell to produce one or more recombinant nucleic acids; (d.) recombining the one or more recombinant nucleic acids with each other or with the one or more first additional nucleic acids or with one or more second additional nucleic acids to produce one or more additional recombinant nucleic acids; and, (e.) selecting or screening the one or more recombinant nucleic acids or the one or more additional recombinant nucleic acids for one or more desirable trait or property.

4. The method of claim 3, wherein step (a) comprises producing fragments of at least two corresponding nucleic acids, hybridizing the resulting fragments; and, elongating the resulting hybridized fragments to produce the transferrable nucleic acids.

5. The method of claim 3, wherein step (a) comprises producing fragments derived from more than one source from nature.

6. The method of claim 3, wherein step (a) comprises producing fragments derived from more than one species.

7. The method of claim 6, wherein said elongating comprises initially extending the hybridized fragments with a first polymerase, denaturing the resulting initially extended hybridized fragments, re-hybridizing the resulting single-stranded initially extended fragments and extending the resulting re-hybridized initially extended fragments with the first polymerase, or with a second polymerase, to produce the elongated nucleic acids.

8. The method of claims 2 or 3, wherein the selection or screening step comprises placing cells which comprise the additional recombinant nucleic acids under selective pressure.

9. The method of claim 1 or 3, wherein the transferrable nucleic acids are stably integrated into a genome of the cell.

10. The method of claim 1 or 3, wherein the transferrable nucleic acids are cloned into one or more episomally replicable vectors.

11. The method of claim 10, wherein the episomally replicable vector is capable of stable replication in the cell.

12. The method of claim 1 or 3, wherein the vector comprises a selectable marker.

13. The method of claim 1 or 3, wherein the transferrable nucleic acids are cloned into one or more episomally replicable vectors, wherein the resulting cloned nucleic acids comprise direct or indirect repeats.

14. The method of claim 13, wherein the cloned nucleic acids are recombined in the cell by intra-vector or inter-vector recombination.

15. The method of claim 1 or 3, wherein the transferrable nucleic acids recombine with each other, or with other nucleic acids, via homologous recombination, in the cell.

16. The method of claim 1 or 3, wherein the cell is treated with a chemical or radiological muatgen.

17. The method of claim 1 or 3, wherein the cell is treated with a chemical or radiological muatgen selected from MNU, ENU, MNNG, nitrosourea, BuDR, UV light, ionizing radiation, and a clastogenic agent.

18. The method of claim 1 or 3, wherein the transferrable nucleic acids are transferred into the cell using one or more transfer techniques selected from: electroporation, natural competence, transduction, transfection, lipofection, biolistics and conjugation.

19. The method of claim 1 or 3, wherein the transferrable nucleic acids are single stranded.

20. The method of claim 1 or 3, wherein the transferrable nucleic acids comprise viral sequences.

21. The method of claim 1 or 3, wherein the transferrable nucleic acids are associated with a recombinase prior to or subsequent to transfer into the cell.

22. The method of claim 21, wherein the recombinase is RecA.

23. The method of claim 1 or 3, wherein the cell is a bacterial cell, a yeast cell, or a mammalian cell.

24. The method of claim 1 or 3, further comprising recombining the additional recombinant nucleic acid with itself or with one or more additional selected nucleic acid.

25. The method of claim 1 wherein the single-stranded segments are produced by cleaving the at least two nucleic acids to produce a population of double-stranded fragments, and denaturing the double-stranded fragments to produce the single-stranded segments.

26. The method of claim 1 wherein the overlapping single-stranded segments are produced on a DNA synthesizer.

27. The method of claim 1 wherein the overlapping single-stranded segments are produced by PCR amplification.

28. The method of claim 1 wherein the single-stranded segments are random segments of the polynucleotides.

29. The method of claim 1 wherein the single-stranded segments are

non-random segments of the polynucleotides.

30. The method of claim 25 wherein the fragments are random fragments.

31. The method of claim 25 wherein the fragments are non-random fragments.

32. The method of claim 3, wherein the plurality of transferable nucleic acids comprises mutagenized nucleic acids.

33. The method of claim 32, wherein the mutagenized nucleic acids are produced by error prone PCR.

34. The method of claim 32, wherein the mutagenized nucleic acids are produced by oligonucleotide directed mutagenesis.

35. The method of claim 32, wherein the mutagenized nucleic acids are produced by chemical mutagenesis.

36. The method of claim 3, wherein the plurality of transferable nucleic acids comprises allelic or species variants of a polynucleotide sequence.

L26 ANSWER 18 OF 25 USPATFULL on STN
2001:235312 Compositions for inhibition of membrane fusion-associated events, including human parainfluenza virus transmission.
Barney, Shawn, 106 Branchway Rd., Cary, NC, United States 27502
Lambert, Dennis, 101 Centerville Ct., Cary, NC, United States 27513
Petteway, Stephen Robert, 203 Le Gault Dr., Cary, NC, United States 27513
US 6333395 B1 20011225
APPLICATION: US 1995-474349 19950607 (8)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An isolated peptide consisting of: (a) an amino acid sequence of a 16 to 39 amino acid residue region of a human parainfluenza virus protein, wherein said region is identified by: (i) 4 or 5 **heptad** repeats of an ALLMOTI5 sequence search motif; (ii) 4 or 5 **heptad** repeats of a 107x178x4 sequence search motif; or (iii) a PLZIP sequence search motif, and (b) an amino terminal X, and a carboxy terminal Z in which: X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

2. The peptide of claim 1, wherein the region of the human parainfluenza virus protein is a region of 28 amino acid residues identified by 4 **heptad** repeats of the ALLMOTI5 sequence search motif.

3. The peptide of claim 1, wherein the region of the human parainfluenza virus protein is a region of 35 amino acid residues identified by 5 **heptad** repeats of the ALLMOTI5 sequence search motif.

4. The peptide of claim 1, wherein the region of the human parainfluenza virus protein is a region of 28 amino acid residues identified by 4 **heptad** repeats of the 107x178x4 sequence search motif.

5. The peptide of claim 1, wherein the region of the human parainfluenza virus protein is a region of 35 amino acid residues identified by 5 **heptad** repeats of the 107x178x4 sequence search motif.

6. The peptide of claim 1, wherein the region of the human parainfluenza virus protein is a region identified by a PLZIP sequence search motif.

7. An isolated peptide having the formula: X-TLNNSVALDPIDISIELNKAKSDLEESKEWIRRSN-Z (SEQ ID NO:33); X-LNNSVALDPIDISIELNKAKSDLEESKEWIRRSNQ-Z (SEQ ID NO:34); X-NNSVALDPIDISIELNKAKSDLEESKEWIRRSNQK-Z (SEQ ID NO:35); X-NSVALDPIDISIELNKAKSDLEESKEWIRRSNQKL-Z (SEQ ID NO:36); X-SVALDPIDISIELNKAKSDLEESKEWIRRSNQKLD-Z (SEQ ID NO:37); X-VALDPIDISIELNKAKSDLEESKEWIRRSNQKLDS-Z (SEQ ID NO:38); X-ALDPIDISIELNKAKSDLEESKEWIRRSNQKLDSI-Z (SEQ ID NO:39); X-LDPIDISIELNKAKSDLEESKEWIRRSNQKLDSIG-Z (SEQ ID NO:40); X-DPIDISIELNKAKSDLEESKEWIRRSNQKLDSIGN-Z (SEQ ID NO:41); X-PIDISIELNKAKSDLEESKEWIRRSNQKLDSIGNW-Z (SEQ ID NO:42); X-IDISIELNKAKSDLEESKEWIRRSNQKLDSIGNWH-Z (SEQ ID NO:43); X-DISIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQ-Z (SEQ ID NO:44); X-ISIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQS-Z (SEQ ID NO:45); X-SIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSS-Z (SEQ ID NO:46); X-IELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSST-Z (SEQ ID NO:47); X-ELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSSTT-Z (SEQ ID NO:48); X-TAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQS-Z (SEQ ID NO:49); X-AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSI-Z (SEQ ID NO:50); X-LVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNL-Z (SEQ ID NO:51); X-VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI-Z (SEQ ID NO:52); X-EAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIV-Z (SEQ ID NO:53); X-AKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA-Z (SEQ ID NO:54); X-KQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAI-Z (SEQ ID NO:55); X-QARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIK-Z (SEQ ID NO:56); X-ARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKS-Z (SEQ ID NO:57); X-RSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSV-Z (SEQ ID NO:58); X-SDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQ-Z (SEQ ID NO:59); X-KLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVN-Z (SEQ ID NO:60); X-LKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNK-Z (SEQ ID NO:61); or X-AIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV-Z (SEQ ID NO:62) in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

8. The peptide of claim 7, wherein the peptide has the formula: X-TLNNSVALDPIDISIELNKAKSDLEESKEWIRRSN-Z (SEQ ID NO:33).

9. The peptide of claim 7, wherein the peptide has the formula: X-LNNSVALDPIDISIELNKAKSDLEESKEWIRRSNQ-Z (SEQ ID NO:34).

10. The peptide of claim 7, wherein the peptide has the formula: X-NNSVALDPIDISIELNKAKSDLEESKEWIRRSNQK-Z (SEQ ID NO:35).

11. The peptide of claim 7, wherein the peptide has the formula: X-NSVALDPIDISIELNKAKSDLEESKEWIRRSNQKL-Z (SEQ ID NO:36).

12. The peptide of claim 7, wherein the peptide has the formula: X-SVALDPIDISIELNKAKSDLEESKEWIRRSNQKLD-Z (SEQ ID NO:37).

13. The peptide of claim 7, wherein the peptide has the formula: X-VALDPIDISIELNKAKSDLEESKEWIRRSNQKLDS-Z (SEQ ID NO:38).

14. The peptide of claim 7, wherein the peptide has the formula: X-ALDPIDISIELNKAKSDLEESKEWIRRSNQKLDSI-Z (SEQ ID NO:39).

15. The peptide of claim 7, wherein the peptide has the formula:

X-LDPIDISIELNKAKSDLEESKEWIRRSNQKLDSIG-Z (SEQ ID NO:40).

16. The peptide of claim 7, wherein the peptide has the formula:
X-DPIDISIELNKAKSDLEESKEWIRRSNQKLDSIGN-Z (SEQ ID NO:41).

17. The peptide of claim 7, wherein the peptide has the formula:
X-PIDISIELNKAKSDLEESKEWIRRSNQKLDSIGNW-Z (SEQ ID NO:42).

18. The peptide of claim 7, wherein the peptide has the formula:
X-IDISIELNKAKSDLEESKEWIRRSNQKLDSIGNWH-Z (SEQ ID NO:43).

19. The peptide of claim 7, wherein the peptide has the formula:
X-DISIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQ-Z (SEQ ID NO:44).

20. The peptide of claim 7, wherein the peptide has the formula:
X-ISIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQS-Z (SEQ ID NO:45).

21. The peptide of claim 7, wherein the peptide has the formula:
X-SIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSS-Z (SEQ ID NO:46).

22. The peptide of claim 7, wherein the peptide has the formula:
X-IELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSST-Z (SEQ ID NO:47).

23. The peptide of claim 7, wherein the peptide has the formula:
X-ELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSSTT-Z (SEQ ID NO:48).

24. The peptide of claim 7, wherein the peptide has the formula:
X-TAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQS-Z (SEQ ID NO:49).

25. The peptide of claim 7, wherein the peptide has the formula:
X-AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSI-Z (SEQ ID NO:50).

26. The peptide of claim 7, wherein the peptide has the formula:
X-LVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNL-Z (SEQ ID NO:51).

27. The peptide of claim 7, wherein the peptide has the formula:
X-VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI-Z (SEQ ID NO:52).

28. The peptide of claim 7, wherein the peptide has the formula:
X-EAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIV-Z (SEQ ID NO:53).

29. The peptide of claim 7, wherein the peptide has the formula:
X-AKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA-Z (SEQ ID NO:54).

30. The peptide of claim 7, wherein the peptide has the formula:
X-KQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAI-Z (SEQ ID NO:55).

31. The peptide of claim 7, wherein the peptide has the formula:
X-QARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIK-Z (SEQ ID NO:56).

32. The peptide of claim 7, wherein the peptide has the formula:
X-ARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKS-Z (SEQ ID NO:57).

33. The peptide of claim 7, wherein the peptide has the formula:
X-RSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSV-Z (SEQ ID NO:58).

34. The peptide of claim 7, wherein the peptide has the formula:
X-SDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQ-Z (SEQ ID NO:59).

35. The peptide of claim 7, wherein the peptide has the formula:
X-KLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVN-Z (SEQ ID NO:60).

36. The peptide of claim 7, wherein the peptide has the formula: X-LKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNK-Z (SEQ ID NO:61).

37. The peptide of claim 7, wherein the peptide has the formula: X-AIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV-Z (SEQ ID NO:62).

38. The peptide of claim 1 or 7 wherein X is a hydrophobic group.

39. The peptide of claim 38 wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

40. The peptide of claim 1 or 7 wherein Z is a hydrophobic group.

41. The peptide of claim 40 wherein the hydrophobic group Z is t-butyloxycarbonyl.

42. The peptide of claim 1 or 7 wherein X is a macromolecular carrier group.

43. The peptide of claim 42 wherein the macromolecular carrier group is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

44. The peptide of claim 1 or 7 wherein Z is a macromolecular carrier group.

45. The peptide of claim 44 wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

46. The peptide of claim 42, wherein the macromolecular group X is a peptide group.

47. The peptide of claim 44, wherein the macromolecular group Z is a peptide group.

48. The isolated peptide of claim 1 or 7 wherein X is an acetyl group.

49. The isolated peptide of claim 1 or 7 wherein Z is an amido group.

50. The isolated peptide of claim 1 or 7 wherein X is an acetyl group, and Z is an amido group.

51. An isolated peptide consisting of: (a) an amino acid sequence of a 16 to 39 amino acid residue region of a human parainfluenza virus protein, wherein said region is identified by: (i) 4 or 5 **heptad** repeats of an ALLMOTI5 sequence search motif, (ii) 4 or 5 **heptad** repeats of a 107x78x4 sequence search motif, or (iii) a PLZIP sequence search motif; (b) an amino terminal insertion of about 2 to about 50 human parainfluenza virus protein amino acid residues amino to the region of the human parainfluenza virus protein identified by the sequence search motif; and (c) an amino terminal X and a carboxy terminal Z, in which X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group, and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

52. The isolated peptide of claim 51 wherein X is a hydrophobic group.

53. The isolated peptide of claim 52 wherein the hydrophobic group X is carbobenzoxyl, dansyl or t-butyloxycarbonyl.

54. The isolated peptide of claim 51 wherein Z is a hydrophobic group.

55. The isolated peptide of claim 54 wherein the hydrophobic group Z is t-butyloxycarbonyl.

56. The isolated peptide of claim 51 wherein X is a macromolecular carrier group.

57. The isolated peptide of claim 56 wherein the macromolecular carrier group X is a lipid-fatty acid conjugate, a polyethylene glycol or a carbohydrate moiety.

58. The isolated peptide of claim 56 wherein the macromolecular carrier group X is a peptide group.

59. The isolated peptide of claim 51 wherein Z is a macromolecular carrier group.

60. The isolated peptide of claim 59 wherein the macromolecular carrier group Z is a lipid-fatty acid conjugate, a polyethylene glycol, or a carbohydrate moiety.

61. The isolated peptide of claim 59 wherein the macromolecular carrier group Z is a peptide group.

62. The isolated peptide of claim 51 wherein X is an acetyl group.

63. The isolated peptide of claim 51 wherein Z is an amido group.

64. The isolated peptide of claim 51 wherein X is an acetyl group, and X is an amido group.

65. The isolated peptide of claim 51 wherein the region of the human parainfluenza virus protein is a region of 28 amino acid residues identified by 4 heptad repeats of the ALLMOTI5 sequence search motif.

66. The isolated peptide of claim 51 wherein the region of the human parainfluenza virus protein is a region of 35 amino acid residues identified by 5 heptad repeats of the ALLMOTI5 sequence search motif.

67. The isolated peptide of claim 51 wherein the region of the human parainfluenza virus protein is a region of 28 amino acid residues identified by 4 heptad repeats of the 107x178x4 sequence search motif.

68. The isolated peptide of claim 51 wherein the region of the human parainfluenza virus protein is a region of 35 amino acid residues identified by 5 heptad repeats of the 107x178x4 sequence search motif.

69. The isolated peptide of claim 51 wherein the region of the human parainfluenza virus is a region identified by a PLZIP sequence search motif.

70. An isolated peptide consisting of: (a) an amino acid sequence of a 16 to 39 amino acid residue region of a human parainfluenza virus protein, wherein said region is identified by: (i) 4 or 5 heptad repeats of an ALLMOTI5 sequence search motif, (ii) 4 or 5 heptad repeats of a 107x178x4 sequence search motif, or (iii) a PLZIP sequence search motif; (b) an carboxy terminal insertion of about 2 to about 50 human parainfluenza virus protein amino acid residues carboxy to the region of the human parainfluenza virus protein

identified by the sequence search motif; and (c) an amino terminal X and a carboxy terminal Z, in which X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group, and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

71. The isolated peptide of claim 70 wherein X is a hydrophobic group.

72. The isolated peptide of claim 71 wherein the hydrophobic group X is carbobenzoxyl, dansyl or t-butyloxycarbonyl.

73. The isolated peptide of claim 70 wherein Z is a hydrophobic group.

74. The isolated peptide of claim 73 wherein the hydrophobic group Z is t-butyloxycarbonyl.

75. The isolated peptide of claim 70 wherein X is a macromolecular carrier group.

76. The isolated peptide of claim 75 wherein the macromolecular carrier group X is a lipid-fatty acid coniugate, a **polyethylene glycol** or a carbohydrate moiety.

77. The peptide of claim 75 wherein the macromolecular carrier group X is a peptide group.

78. The isolated peptide of claim 70 wherein Z is a macromolecular carrier group.

79. The isolated peptide of claim 78 wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

80. The isolated peptide of claim 78 wherein the macromolecular carrier group Z is a peptide group.

81. The isolated peptide of claim 70 wherein X is an acetyl group.

82. The isolated peptide of claim 70 wherein Z is an amido group.

83. The isolated peptide of claim 70 wherein X is an acetyl group, and X is an amido group.

84. The isolated peptide of claim 70 wherein the region of the human parainfluenza virus protein is a region of 28 amino acid residues identified by 4 **heptad** repeats of the ALLMOTI5 sequence search motif.

85. The isolated peptide of claim 70 wherein the region of the human parainfluenza virus protein is a region of 35 amino acid residues identified by 5 **heptad** repeats of the ALLMOTI5 sequence search motif.

86. The isolated peptide of claim 70 wherein the region of the human parainfluenza virus protein is a region of 28 amino acid residues identified by 4 **heptad** repeats of the 107x178x4 sequence search motif.

87. The isolated peptide of claim 70 wherein the region of the human parainfluenza virus protein is a region of 35 amino acid residues identified by 5 **heptad** repeats of the 107x178x4 sequence search motif.

88. The isolated peptide of claim 70 wherein the region of the human

parainfluenza virus is a region identified by a PLZIP sequence search motif.

89. An isolated peptide consisting of: (a) an amino acid sequence of a 16 to 39 amino acid residue region of a human parainfluenza virus protein, wherein said region is identified by: (i) 4 or 5 **heptad** repeats of an ALLMOTIS sequence search motif, (ii) 4 or 5 **heptad** repeats of a 107x178x4 sequence search motif, or (iii) a PLZIP sequence search motif; (b) an amino terminal insertion of about 2 to about 50 human parainfluenza virus protein amino acid residues amino to the region of the human parainfluenza virus protein identified by the sequence search motif; (c) an carboxy terminal insertion of about 2 to about 50 human parainfluenza virus protein amino acid residues carboxy to the region of the human parainfluenza virus protein identified by the sequence search motif, and (d) an amino terminal X and a carboxy terminal Z, in which X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group, and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

90. The isolated peptide of claim 89 wherein X is a hydrophobic group.

91. The isolated peptide of claim 90 wherein the hydrophobic group X is carbobenzoxyl, dansyl or t-butyloxycarbonyl.

92. The isolated peptide of claim 89 wherein Z is a hydrophobic group.

93. The isolated peptide of claim 92 wherein the hydrophobic group Z is t-butyloxycarbonyl.

94. The isolated peptide of claim 89 wherein X is a macromolecular carrier group.

95. The isolated peptide of claim 94 wherein the macromolecular carrier group X is a lipid-fatty acid **conjugate**, a **polyethylene glycol** or a carbohydrate moiety.

96. The isolated peptide of claim 94 wherein the macromolecular carrier group X is a peptide group.

97. The isolated peptide of claim 89 wherein Z is a macromolecular carrier group.

98. The isolated peptide of claim 97 wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugates** a **polyethylene glycol**, or a carbohydrate moiety.

99. The isolated peptide of claim 97 wherein the macromolecular carrier group Z is a peptide group.

100. The isolated peptide of claim 89 wherein X is an acetyl group.

101. The isolated peptide of claim 89 wherein Z is an amido group.

102. The isolated peptide of claim 89 wherein X is an acetyl group, and X is an amido group.

103. The isolated peptide of claim 89 wherein the region of the human parainfluenza virus protein is a region of 28 amino acid residues identified by 4 **heptad** repeats of the ALLMOTIS sequence search motif.

104. The isolated peptide of claim 89 wherein the region of the human

parainfluenza virus protein is a region of 35 amino acid residues identified by 5 **heptad** repeats of the ALLMOTI5 sequence search motif.

105. The isolated peptide of claim 89 wherein the region of the human parainfluenza virus protein is a region of 28 amino acid residues identified by 4 **heptad** repeats of the 107x178x4 sequence search motif.

106. The isolated peptide of claim 89 wherein the region of the human parainfluenza virus protein is a region of 35 amino acid residues identified by 5 **heptad** repeats of the 107x178x4 sequence search motif.

107. The isolated peptide of claim 89 wherein the region of the human parainfluenza virus is a region identified by a PLZIP sequence search motif.

L26 ANSWER 19 OF 25 USPATFULL on STN
2001:152769 Methods for generating polynucleotides having desired characteristics by iterative selection and recombination.
Stemmer, Willem P. C., Los Gatos, CA, United States
Crameri, Andreas, Mountain View, CA, United States
Maxygen, Inc., Redwood City, CA, United States (U.S. corporation)
US 6287861 B1 20010911
APPLICATION: US 1998-133508 19980812 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for evolving a polynucleotide for acquisition of a desired functional property, comprising: (1) providing a library of variant forms of a polynucleotide, some of which are components of a vector, and some of which are not components of a vector, (2) introducing the library of variant forms into a population of cells, (3) propagating the cells under conditions whereby recombination occurs between the variant forms that are components of a vector and the variant forms that are not components of a vector to generate recombinant forms of the polynucleotide; (4) selecting or screening the recombinant forms of the polynucleotide to identify at least one recombinant form of the polynucleotide having evolved toward a desired property.

2. The method of claim 1, wherein the variant forms that are components of a vector are components of a phage vector.

3. The method of claim 1, wherein the variant forms that are components of a vector are components of a plasmid vector.

4. The method of claim 1, wherein the library of variant forms are introduced by a process selected from the group consisting of electroporation, lipofection, biolisitics, and **conjugation**.

5. The method of claim 1, wherein the variant forms that are components of a vector are introduced into cells before the variant forms that are not components of a vector.

6. The method of claim 1, further comprising isolating the recombinant forms and repeating steps (1)-(4) wherein the library of variant forms comprises the recombinant forms.

7. The method of claim 1, wherein the variants of the polynucleotide are naturally occurring variants.

8. The method of claim 7, wherein the naturally occurring variant of the polynucleotide encode naturally occurring polypeptides.

9. The method of claim 7, wherein the naturally occurring variants of a polynucleotide comprise human polynucleotides.

10. The method of claim 7, wherein the naturally occurring variants of a polynucleotide comprise bacterial polynucleotides.

11. The method of claim 7, wherein the naturally occurring variants of a polynucleotide comprise a plant polynucleotides.

12. The method of claim 7, wherein the naturally occurring variants of a polynucleotide comprise a fungal polynucleotides.

13. The method of claim 7, wherein the naturally occurring variants of a polynucleotide comprise animal polynucleotides.

14. The method of claim 7, wherein the naturally occurring variants of a polynucleotide comprise viral polynucleotides.

15. The method of claim 7, wherein the naturally occurring variants of a polynucleotide comprise nonallelic gene sequences from the same species having sufficient sequence similarity for annealing of segments of different variants.

16. The method of claim 7, wherein the naturally occurring variants of a polynucleotides comprise allelic variants of a gene.

17. The method of claim 7, wherein the naturally occurring variants of a polynucleotide comprises species variants of a gene.

18. The method of claim 1, wherein the desired property is capacity to bind a receptor.

19. The method of claim 1, wherein the desired property is drug resistance.

20. The method of claim 1, wherein the desired property is a therapeutic activity.

21. The method of claim 1, wherein the recombinant polynucleotide is screened for suitable as an agent for gene therapy.

22. The method of claim 1, wherein the recombinant polynucleotide is screened for suitability as an agent for anti-neoplastic therapy.

23. The method of claim 1, wherein the recombinant polynucleotide is screened for suitability as an agent for DNA-based vaccination.

24. The method of claim 1, further comprising shuffling a recombinant polynucleotide with the desired property with a naturally occurring polynucleotide to eliminate variations between the recombinant polynucleotide and the naturally occurring polynucleotide that do not contribute to the desired property of the recombinant polynucleotide.

25. The method of claim 1, further comprising fragmenting the variants that are not components of a vector before introducing the variants into the cells.

26. The method of claim 25, wherein the variants are randomly fragmented.

27. The method of claim 1, wherein the library of variant forms is provided by conducting a polynucleotide amplification process on overlapping segments of a population of polynucleotides under conditions whereby one segment serves as a template for extension of another segment to generate a population of variant forms.

28. A method for evolving a polynucleotide for acquisition of a desired functional property, comprising: (1) providing a mixed population of variant forms of a polynucleotide, each form incorporated in a separate copy of the same vector; (2) introducing the mixed population of variant forms into a population of cells, whereby some cells receive from the mixed population at least two different variant forms of the polynucleotide incorporated on separate copies of the vector, which recombine with each other, thereby forming a library of recombinant forms of the polynucleotide incorporated in separate copies of the vector; (3) selecting or screening the recombinant forms of the polynucleotides to identify at least one recombinant form of the polynucleotide having evolved toward the desired functional property.

29. The method of claim 28, wherein the vector is a phage vector.

30. The method of claim 28, wherein the vector is a plasmid vector.

31. The method of claim 28, wherein the library of variant forms are introduced by a process selected from the group consisting of electroporation, lipofection, biolistics, and **conjugation**.

32. The method of claim 28, further comprising isolating recombinant forms having evolved toward the desired functional property and repeating steps (1)-(3) wherein the variant forms comprise the recombinant forms.

33. The method of claim 28, wherein the variants of the polynucleotide are naturally occurring variants.

34. The method of claim 33, wherein the naturally occurring variants of the polynucleotide encode naturally occurring polypeptides.

35. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprise human polynucleotides.

36. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprise bacterial polynucleotides.

37. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprise a plant polynucleotides.

38. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprise a fungal polynucleotides.

39. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprise animal polynucleotides.

40. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprise viral polynucleotides.

41. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprise nonallelic gene sequences from the same species having sufficient sequence similarity for annealing of segments of different variants.

42. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprise allelic variants of a gene.

43. The method of claim 33, wherein the naturally occurring variants of a polynucleotide comprises species variants of a gene.

44. The method of claim 28, wherein the desired functional property is capacity to bind a receptor.

45. The method of claim 28, wherein the desired functional property is drug resistance.

46. The method of claim 28, wherein the desired functional property is a therapeutic activity.

47. The method of claim 28, wherein the recombinant polynucleotide is screened for suitability as an agent for gene therapy.

48. The method of claim 28, wherein the recombinant polynucleotide is screened for suitability as an agent for anti-neoplastic therapy.

49. The method of claim 28, wherein the recombinant polynucleotide is screened for suitability as an agent for DNA-based vaccination.

50. The method of claim 28, further comprising shuffling a recombinant polynucleotide with the desired functional property with a naturally occurring polynucleotide to eliminate variations between the recombinant polynucleotide and the naturally occurring polynucleotide that do not contribute to the desired functional property of the recombinant polynucleotide.

51. A method for evolving a polynucleotide for acquisition of a desired functional property, comprising: (1) providing variant forms of a polynucleotide, each form incorporated in a vector; (2) introducing the variant forms into a population of cells, whereby some cells receive at least two different variant forms of the polynucleotide, whereby the different variant forms of the polynucleotides recombine to form a library of recombinant forms of the polynucleotide incorporated in the vector; (3) selecting or screening for recombinant forms of the polynucleotides having evolved toward the desired functional property; (4) repeating (2) and (3) with further variant forms of the polynucleotide comprising a subset of the recombinant forms having evolved toward the desired functional property, until a recombinant form of a polynucleotide has acquired the desired functional property.

52. The method of claim 51, wherein the vector is a phage vector.

53. The method of claim 51, wherein the vector is a plasmid vector.

54. The method of claim 51, wherein the variant forms of a polynucleotide are introduced by a process selected from the group consisting of electroporation, lipofection, biolistics, and conjugation.

55. The method of claim 51, wherein the variant forms of the polynucleotide are naturally occurring variants.

56. The method of claim 55, wherein the naturally occurring variants of the polynucleotide encode naturally occurring polypeptides.

57. The method of claim 56, wherein the naturally occurring variants of a polynucleotide comprise human polynucleotides.

58. The method of claim 56, wherein the naturally occurring variants of a polynucleotide comprise bacterial polynucleotides.

59. The method of claim 56, wherein the naturally occurring variants of a polynucleotide comprise plant polynucleotides.

60. The method of claim 56, wherein the naturally occurring variants of a polynucleotide comprise fungal polynucleotides.

61. The method of claim 56, wherein the naturally occurring variants of a polynucleotide comprise animal polynucleotides.

62. The method of claim 56, wherein the naturally occurring variants of a polynucleotide comprise viral polynucleotides.

63. The method of claim 56, wherein the naturally occurring variants of a polynucleotide comprise nonallelic gene sequences from the same species having sufficient sequence similarity for annealing of segments of different variants.

64. The method of claim 56, wherein the naturally occurring variants of a polynucleotides comprise allelic variants of a gene.

65. The method of claim 56, wherein the naturally occurring variants of a polynucleotide comprises species variants of a gene.

66. The method of claim 51, wherein the desired functional property is capacity to bind a receptor.

67. The method of claim 51, wherein the desired functional property is drug resistance.

68. The method of claim 51, wherein the desired functional property is a therapeutic activity.

69. The method of claim 51, wherein the recombinant polynucleotide is screened for suitability as an agent for gene therapy.

70. The method of claim 51, wherein the recombinant polynucleotide is screened for suitability as an agent for anti-neoplastic therapy.

71. The method of claim 51, wherein the recombinant polynucleotide is screened for suitability as an agent for DNA-based vaccination.

72. The method of claim 51, further comprising shuffling a recombinant polynucleotide with the desired functional property with a naturally occurring polynucleotide to eliminate variations between the recombinant polynucleotide and the naturally occurring polynucleotide that do not contribute to the desired functional property of the recombinant polynucleotide.

73. A method of evolving a polynucleotide sequence toward a desired functional property, comprising: (1) recombining variant forms of a polynucleotide sequence in a host cell, at least some of which forms are provided in cell-free form before introduction into the host cell; (2) selecting or screening for recombinant forms of the polynucleotide sequence that have evolved toward the desired functional property; (3) recombining selected or screened recombinant forms having evolved toward the desired functional property with each other to generate further recombinant forms; (4) selecting or screening for further recombinant forms of the polynucleotide sequence that have evolved toward the desired functional property.

74. The method of claim 73, wherein some of the variant forms are stably integrated in the host cell.

75. The method of claim 73, wherein the variant forms in cell-free form are provided as components of a phage vector.

76. The method of claim 73, wherein the variant forms in cell-free form are provided as components of a plasmid vector.

77. The method of claim 73, wherein the variant forms in cell-free form are introduced into the host cell by a process selected from the group consisting of electroporation, lipofection, biolistics, and conjugation.

78. The method of claim 77, wherein the variant forms are naturally occurring variants.

79. The method of claim 78, wherein the naturally occurring variant of the polynucleotide encode naturally occurring polypeptides.

80. The method of claim 78, wherein the naturally occurring variants of a polynucleotide comprise human polynucleotides.

81. The method of claim 78, wherein the naturally occurring variants of a polynucleotide comprise bacterial polynucleotides.

82. The method of claim 78, wherein the naturally occurring variants of a polynucleotide comprise a plant polynucleotides.

83. The method of claim 78, wherein the naturally occurring variants of a polynucleotide comprise fungal polynucleotides.

84. The method of claim 78, wherein the naturally occurring variants of a polynucleotide comprise animal polynucleotides.

85. The method of claim 78, wherein the naturally occurring variants of a polynucleotide comprise viral polynucleotides.

86. The method of claim 78, wherein the naturally occurring variants of a polynucleotide comprise nonallelic gene sequences from the same species having sufficient sequence similarity for annealing of segments of different variants.

87. The method of claim 78, wherein the naturally occurring variants of a polynucleotides comprise allelic variants of a gene.

88. The method of claim 78, wherein the naturally occurring variants of a polynucleotide comprises species variants of a gene.

89. The method of claim 73, wherein the desired functional property is capacity to bind a receptor.

90. The method of claim 73, wherein the desired functional property is drug resistance.

91. The method of claim 73, wherein the desired functional property is a therapeutic activity.

92. The method of claim 73, wherein desired functional property is suitability as an agent for gene therapy.

93. The method of claim 73, wherein the desired functional property is

suitability as an agent for anti-neoplastic therapy.

94. The method of claim 73, wherein the desired functional property is suitability as an agent for DNA-based vaccination.

L26 ANSWER 20 OF 25 USPATFULL on STN
2001:67794 Human respiratory syncytial virus peptides with antifusogenic and antiviral activities.
Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6228983 B1 20010508
APPLICATION: US 1995-485264 19950607 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An isolated peptide consisting of an amino acid sequence of a 16 to 39 amino acid region of a human respiratory syncytial virus protein, wherein said region is identified by an ALLMOTIS, 107x178x4, or PLZIP sequence search motif, said peptide further consisting of an amino terminal X, and a carboxy terminal Z in which: X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

2. A peptide having the formula: ##STR6## in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group for an effective period of time so that no infection of the cell by the virus occurs.

3. The peptide of claim 1 or 2 wherein X is a hydrophobic group.

4. The peptide of claim 3 wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

5. The peptide of claim 1 or 2 wherein Z is a hydrophobic group.

6. The peptide of claim 5 wherein the hydrophobic group Z is t-butyloxycarbonyl.

7. The peptide of claim 1 or 2 wherein X is a macromolecular carrier group.

8. The peptide of claim 7 wherein the macromolecular carrier group is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

9. The peptide of claim 1 or 2 wherein Z is a macromolecular carrier group.

10. The peptide of claim 9 wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

11. The peptide of claim 2 wherein at least one bond linking adjacent amino acid residues is a non-peptide bond.

12. The peptide of claim 11 wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

13. The peptide of claim 2 wherein at least one amino acid residue is in a D-isomer configuration.

14. The peptide of claim 2, wherein the peptide has the formula: X-TSVITIELSNIKENKCNGTDAKVKLIKQELDKYKN-Z (SEQ ID NO. 125).

15. The peptide of claim 2, wherein the peptide has the formula: X-SVITIELSNIKENKCNGTDAKVKLIKQELDKYKNA-Z (SEQ ID NO. 126).

16. The peptide of claim 2, wherein the peptide has the formula: X-VITIELSNIKENKCNGTDAKVKLIKQELDKYKNAV-Z (SEQ ID NO. 210).

17. The peptide of claim 2, wherein the peptide has the formula: X-VAVSKVLHLEGEVNKIALLSTNKAVVSLSNGVS-Z (SEQ ID NO. 20).

18. The peptide of claim 2, wherein the peptide has the formula: X-AVSKVLHLEGEVNKIALLSTNKAVVSLSNGVSV-Z (SEQ ID NO. 21).

19. The peptide of claim 2, wherein the peptide has the formula: X-VSKVLHLEGEVNKIALLSTNKAVVSLSNGVSVL-Z (SEQ ID NO. 22).

20. The peptide of claim 2, wherein the peptide has the formula: X-SKVLHLEGEVNKIALLSTNKAVVSLSNGVSVLT-Z (SEQ ID NO. 23).

21. The peptide of claim 2, wherein the peptide has the formula: X-KVLHLEGEVNKIALLSTNKAVVSLSNGVSVLTS-Z (SEQ ID NO. 24).

22. The peptide of claim 2, wherein the peptide has the formula: X-LEGEVNKIALLSTNKAVVSLSNGVSVLTSKVLD-Z (SEQ ID NO. 25).

23. The peptide of claim 2, wherein the peptide has the formula: X-GEVNKIALLSTNKAVVSLSNGVSVLTSKVLDLK-Z (SEQ ID NO. 26).

24. The peptide of claim 2, wherein the peptide has the formula: X-EVNKIALLSTNKAVVSLSNGVSVLTSKVLDLKN-Z (SEQ ID NO. 27).

25. The peptide of claim 2, wherein the peptide has the formula: X-VNKIALLSTNKAVVSLSNGVSVLTSKVLDLKNY-Z (SEQ ID NO. 28).

26. The peptide of claim 2, wherein the peptide has the formula: X-NKIALLSTNKAVVSLSNGVSVLTSKVLDLKNYI-Z (SEQ ID NO. 29).

27. The peptide of claim 2, wherein the peptide has the formula: X-KIALLSTNKAVVSLSNGVSVLTSKVLDLKNYID-Z (SEQ ID NO. 30).

28. The peptide of claim 2, wherein the peptide has the formula: X-IALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDK-Z (SEQ ID NO. 31).

29. The peptide of claim 2, wherein the peptide has the formula: X-ALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ-Z (SEQ ID NO. 32).

30. The peptide of claim 2, wherein the peptide has the formula: X-DEFDASISQVNEKINQSLAFIRKSDELL-Z (SEQ ID NO. 211).

31. The peptide of claim 2, wherein the peptide has the formula: X-IINFYDPLVFPSDEFDASISQVNEKINQSLAFIRK-Z (SEQ ID NO. 212).

32. The peptide of claim 2, wherein the peptide has the formula:

X-INFYDPLVFPSDEFDASISQVNEKINQSLAFIRKS-Z (SEQ ID NO. 213).

33. The peptide of claim 2, wherein the peptide has the formula:
X-FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDE-Z (SEQ ID NO. 214).

34. The peptide of claim 2, wherein the peptide has the formula:
X-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-Z (SEQ ID NO. 215).

35. The peptide of claim 2, wherein the peptide has the formula:
X-DPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL-Z (SEQ ID NO. 216).

36. The peptide of claim 2, wherein the peptide has the formula:
X-PLVFPSDEFDASISQVNEKINQSLAFIRKSDELLH-Z (SEQ ID NO. 217).

37. The peptide of claim 2, wherein the peptide has the formula:
X-LVFPSDEFDASISQVNEKINQSLAFIRKSDELLHN-Z (SEQ ID NO. 218).

38. The peptide of claim 2, wherein the peptide has the formula:
X-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-Z (SEQ ID NO. 219).

39. The peptide of claim 2, wherein the peptide has the formula:
X-FPSDEFDASISQVNEKINQSLAFIRKSDELLHNVN-Z (SEQ ID NO. 220).

40. The peptide of claim 2, wherein the peptide has the formula:
X-PSDEFDASISQVNEKINQSLAFIRKSDELLHNVNA-Z (SEQ ID NO. 221).

41. The peptide of claim 2, wherein the peptide has the formula:
X-SDEFDASISQVNEKINQSLAFIRKSDELLHNVNAG-Z (SEQ ID NO. 222).

42. The peptide of claim 2, wherein the peptide has the formula:
X-DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-Z (SEQ ID NO. 223).

43. The peptide of claim 2, wherein the peptide has the formula:
X-EFDASISQVNEKINQSLAFIRKSDELLHNVNAGKS-Z (SEQ ID NO. 224).

44. The peptide of claim 2, wherein the peptide has the formula:
X-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-Z (SEQ ID NO. 225).

45. The peptide of claim 2, wherein the peptide has the formula:
X-DASISQVNEKINQSLAFIRKSDELLHNVNAGKSTT-Z (SEQ ID NO. 226).

46. The peptide of claim 2, wherein the peptide has the formula:
X-FDASISQVNEKINQSLAFIRKSDELLHNVNAGK-Z (SEQ ID NO. 143).

47. The peptide of claim 2, wherein the peptide has the formula:
X-FDASISQVNEKINQSLAFIRKSDELLHNVNA-Z (SEQ ID NO. 227).

48. The peptide of claim 2, wherein the peptide has the formula:
X-FDASISQVNEKINQSLAFIRKSDELLHNV-Z (SEQ ID NO. 228).

49. The peptide of claim 2, wherein the peptide has the formula:
X-FDASISQVNEKINQSLAFIRKSDELLH-Z (SEQ ID NO. 229).

50. The peptide of claim 2, wherein the peptide has the formula:
X-FDASISQVNEKINQSLAFIRKSDEL-Z (SEQ ID NO. 230).

51. The peptide of claim 2, wherein the peptide has the formula:
X-ASISQVNEKINQSLAFIRKSDELLHNVNAGKST-Z (SEQ ID NO. 144).

52. The peptide of claim 2, wherein the peptide has the formula:
X-ISQVNEKINQSLAFIRKSDELLHNVNAGKST-Z (SEQ ID NO. 231).

53. The peptide of claim 2, wherein the peptide has the formula: X-QVNEKINQSLAFIRKSDELLHNVNAGKST-Z (SEQ ID NO. 232).

54. The peptide of claim 1, wherein the region of the human respiratory syncytial virus protein consists of a region of 28 amino acid residues identified by the ALLMOTI5 sequence search motif.

55. The peptide of claim 1, wherein the region of the human respiratory syncytial virus protein consists of a region of 35 amino acid residues identified by the ALLMOTI5 sequence search motif.

56. The peptide of claim 1, wherein the region of the human respiratory syncytial virus protein is consists of a region of 28 amino acid residues identified by the 107x178x4 sequence search motif.

57. The peptide of claim 1, wherein the region of the human respiratory syncytial virus protein consists of a region of 35 amino acid residues identified by the 107x178x4 sequence search motif.

58. The peptide of claim 1, wherein the region of the human respiratory syncytial virus protein is identified by the PLZIP sequence search motif.

59. The peptide of claim 7, wherein the macromolecular group is a peptide group.

60. The peptide of claim 59, wherein the peptide group is about 2 to about 50 amino acid residues amino to the region of the human respiratory syncytial virus protein identified by the ALLMOTI5, 107x178x4, or PLZIP sequence search motif.

61. The peptide of claim 9, wherein the macromolecular group is a peptide group.

62. The peptide of claim 61, wherein the peptide group is about 2 to about 50 amino acid residues amino to the region of the human respiratory syncytial virus protein identified by the ALLMOTI5, 107x178x4, or PLZIP sequence search motif.

L26 ANSWER 21 OF 25 USPATFULL on STN
2000:121322 Methods for generating polynucleotides having desired characteristics by iterative selection and recombination.
Stemmer, Willem P. C., Los Gatos, CA, United States
Maxygen, Inc., Redwood City, CA, United States (U.S. corporation)
US 6117679 20000912
APPLICATION: US 1996-621859 19960325 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of shuffling polynucleotides, comprising: conducting a polynucleotide amplification process on overlapping segments of a population of variant polynucleotides under conditions whereby one segment serves as a template for extension of another segment, to generate a population of recombinant polynucleotides; and selecting or screening a recombinant polynucleotide for a desired property, wherein the amplification process is performed in the presence of an agent that promotes annealing of the overlapping segments.

2. The method of claim 1, wherein the agent is selected from the group consisting of, a cationic detergent, an exonuclease and a recombinogenic protein.

3. The method of claim 1, wherein the agent is recA.

4. A method of shuffling polynucleotides, comprising: conducting a polynucleotide amplification process on overlapping segments of a population of variant polynucleotides under conditions whereby one segment serves as a template for extension of another segment, to generate a population of recombinant polynucleotides; and selecting or screening a recombinant polynucleotide for a desired property wherein the population of variant polynucleotides is converted into overlapping segments of a desired size by replication of the polynucleotide in the presence of UTP, cleavage of the replicated polynucleotide with UDG glycosylase and denaturation.

5. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein at least one recombining step is between different forms of the polynucleotide sequence in separate plasmid vectors.

6. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property wherein at least one recombining step is between a first form of the polynucleotide sequence in a viral vector and a second form of the polynucleotide sequence in a plasmid vector.

7. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein at least one recombining step is between different forms of the polynucleotide sequences in separate viral vectors.

8. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein at least one recombining step is between a first form of the polynucleotide and a second form of the polynucleotide that is a component of a chromosome in a host cell.

9. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein the first form of the polynucleotide is in a plasmid vector.

10. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein the first form of the polynucleotide is in a viral vector.

11. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein different forms of the polynucleotide are contained in a population of

cells and the cells are exposed to an electric field promoting exchange of the different forms between the cells.

12. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein different forms of the polynucleotide are contained in a collection of cells and the different forms are exchanged between cells by **conjugation**.

13. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein at least one recombining step is effected by nonhomologous recombination of different forms of the polynucleotide.

14. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein the polynucleotide has introns and exons and at least one recombining step is effected by homologous recombination between introns of different forms of the polynucleotide.

15. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one

further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein at least one recombining step is performed in vivo and at least one recombining step is performed in vitro.

16. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein at least two recombining steps are performed in vitro.

17. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property and (6) selecting for recombinant or further recombinant polynucleotides relative to unrecombined forms of the polynucleotide sequence after at least one recombining step.

18. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein at least one recombining step is performed in a mutator host cell or a host cell exposed to a mutagen.

19. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the

same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein the polynucleotide sequence is a gene.

20. The method of claim 19, wherein at least one form of the polynucleotide is in purified form.

21. The method of claim 19, wherein at least one recombining step is performed in vivo.

22. (Amended) The method of claim 19, wherein at least two recombining steps are performed in vivo.

23. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein the further recombinant polynucleotide evolves at a frequency of at least 1 mutation per 106 positions per cycle.

24. A method of evolving a polynucleotide sequence toward a desired property comprising: (1) recombining at least first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence; (2) screening at least a first recombinant form of the polynucleotide from the library for evolution toward the desired property; (3) recombining the first recombinant form of the polynucleotide with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library of recombinant polynucleotides; (4) screening at least one further recombinant polynucleotide from the further library of recombinant polynucleotides that has further evolved toward the desired property; (5) repeating (3) and (4), as necessary, until the further recombinant polynucleotide has acquired the desired property, wherein the second form of the polynucleotide is produced by mutagenesis of the first form of the polynucleotide.

25. The method of claim 16, wherein the in vitro recombining steps comprise: conducting a polynucleotide amplification process on overlapping single-stranded segments of a population of variant polynucleotidcs under conditions whereby one segment serves a s a template for extension of another segment to generate a population of recomnbinant polynucleotides.

26. The method of claim 19, wherein at least one recombining step comprises: conducting a polynucleotide amplification process on overlapping segments of a population of variant polynucleotides under conditions whereby one segment serves as a template for extension of another segment, to generate a population of recombinant polynucleotides.

27. A method of shuffling polynucleotides, comprising: initiating a polynucleotide amplification process on overlapping segments of a population of variant polynucleotides under conditions whereby one segment serves as a template for extension of another segment, to generate a population of recombinant polynuclcotides: and selecting or screening a recombinant polynucleotide for a desired property.

28. The method of any one of claims 25, 26 and 27, wherein the overlapping segments are produced by cleavage of the population of variant polynucleotides.

29. The method of any one of claims 25, 26, and 27, wherein the cleavage is by DNaseI digestion.

30. The method of any one of claims 25, 26 and 27, wherein the overlapping segments are produced by chemical synthesis.

31. The method of any one of claims 25, 26 and 27, wherein the overlapping segments are produced by amplification of the population of polynucleotides.

32. The method of any one of claims 25, 26 and 27, wherein the population of variant polynucleotides are allelic variants.

33. The method of any one of claims 25, 26 and 27, wherein the population of variant polynucleotides are species variants.

34. The method of claim 25, wherein the overlapping single-stranded segments are produced by: cleaving the population of variant polynucleotides to produce overlapping double-stranded polynucleotide fragments; and denaturing the double-stranded polynucleotide fragments to produce the overlapping single-stranded polynucleotide segments.

35. The method of claim 34, wherein the variant polynucleotides are DNA and the cleaving is performed by DNase digestion.

L26 ANSWER 22 OF 25 USPATFULL on STN
2000:95093 Isolated peptides derived from the Epstein-Barr virus containing fusion inhibitory domains.
Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6093794 20000725
APPLICATION: US 1995-471913 19950607 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An isolated peptide consisting of an amino acid sequence of a 16 to 39 amino acid residue region of an Epstein-Barr virus protein, wherein said region is identified by an ALLMOTI5, 107x178x4, or PLZIP sequence search motif, said peptide further consists of an amino terminal X, and a carboxy terminal Z in which: X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group a hydrophobic group, or a macromolecular carrier group.

2. An isolated peptide having the formula: X-SELEIKRYKNRVASKRKCRAKFKQLLQHYREVAAAK-Z (SEQ ID NO.210);

X-CRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCP-Z (SEQ ID NO.211);
X-AKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSL-Z (SEQ ID NO.212);
X-KQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVD-Z (SEQ ID NO.213); or
X-QLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-Z (SEQ ID NO.214); in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

3. The peptide of claim 1 or 2 wherein X is a hydrophobic group.

4. The peptide of claim 3 wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

5. The peptide of claim 1 or 2 wherein Z is a hydrophobic group.

6. The peptide of claim 5 wherein the hydrophobic group Z is t-butyloxycarbonyl.

7. The peptide of claim 1 or 2 wherein X is a macromolecular carrier group.

8. The peptide of claim 7 wherein the macromolecular carrier group is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

9. The peptide of claim 1 or 2 wherein Z is a macromolecular carrier group.

10. The peptide of claim 9 wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

11. The peptide of claim 1 or 2 wherein at least one bond linking adjacent amino acid residues is a non-peptide bond.

12. The peptide of claim 11 wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

13. The peptide of claim 1 or 2 wherein at least one amino acid residue is in a D-isomer configuration.

14. The peptide of claim 7 wherein the macromolecular group is a peptide group.

15. The peptide of claim 14 wherein the peptide group is about 2 to about 50 amino acid residues amino to the Epstein-Barr virus protein identified by the ALLMOTI5, 107x178x4, or PLZIP sequence search motif.

16. The peptide of claim 9 wherein the macromolecular group is a peptide group.

17. The peptide of claim 16 wherein the peptide group is about 2 to about 50 amino acid residues amino to the Epstein-Barr virus protein identified by the ALLMOTI5, 107x178x4, or PLZIP sequence search motif.

18. The peptide of claim 1 wherein the region of the Epstein-Barr virus protein consists of a region of 28 amino acid residues identified by the ALLMOTI5 sequence search motif.

19. The peptide of claim 1 wherein the region of the Epstein-Barr virus protein consists of a region of 35 amino acid residues identified by the ALLMOTI5 sequence search motif.

20. The peptide of claim 1 wherein the region of the Epstein-Barr virus protein consists of a region of 28 amino acid residues identified by the 107x178x4 sequence search motif.

21. The peptide of claim 1 wherein the region of the Epstein-Barr virus protein consists of a region of 35 amino acid residues identified by the 107x178x4 sequence search motif.

22. The peptide of claim 1 wherein the region of the Epstein-Barr virus protein is identified by the PLZIP sequence search motif.

23. The peptide of claim 2 wherein the peptide has the formula: X-SELEIKRYKNRVASKRKCRAKFKQLLQHYREVAAAK-Z (SEQ ID NO.210).

24. The peptide of claim 2 wherein the peptide has the formula: X-CRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCP-Z (SEQ ID NO.211).

25. The peptide of claim 2 wherein the peptide has the formula: X-AKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSL-Z (SEQ ID NO.212).

26. The peptide of claim 2 wherein the peptide has the formula: X-KQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVD-Z (SEQ ID NO.213).

27. The peptide of claim 2 wherein the peptide has the formula: X-QLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-Z (SEQ ID NO.214).

L26 ANSWER 23 OF 25 USPATFULL on STN
2000:31403 Compositions containing nucleic acids and ligands for therapeutic treatment.
Baird, J. Andrew, San Diego, CA, United States
Chandler, Lois Ann, Encinitas, CA, United States
Sosnowski, Barbara A., Coronado, CA, United States
Selective Genetics, Inc., La Jolla, CA, United States (U.S. corporation)
US 6037329 20000314
APPLICATION: US 1996-718904 19960924 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A gene delivery composition having the formula: polypeptide that binds to a fibroblast growth factor (FGF) receptor-nucleic acid binding domain-nucleic acid molecule, wherein: the nucleic acid binding domain being chemically **conjugated** or fused to the polypeptide that binds to an FGF receptor, the nuclcic acid molecule being bound to the nucleic acid binding domain; and wherein the gene delivery composition binds to an FGF receptor and is internalized specifically in cells bearing the FGF receptor.

2. The composition of claim 1, wherein the nucleic acid molecule is a cytocide-encoding agent.

3. The composition of claim 2 wherein the cytocide encoding agent encodes a ribosome inactivating protein.

4. The composition of claim 3 wherein the ribosome inactivating protein is saporin.

5. The composition of claim 3 wherein the ribosome inactivating protein is gelonin.

6. The composition of claim 2 wherein the cytocide encoding agent encodes a protein that inhibits elongation factor 2.

7. The composition of claim 6 wherein the protein is diphtheria toxin.

8. The composition of claim 1, wherein the nucleic acid molecule is a prodrug-encoding agent.

9. The composition of either of claims 1, 2, or 8 wherein the polypeptide that binds to the FGF receptor is FGF-2 and the nucleic acid binding domain is poly-L-lysine.

10. The composition of either of claims 1, 2, or 8 wherein the nucleic acid binding domain is a transcription factor.

11. The composition of either of claims 1, 2, or 8 wherein the nucleic acid binding domain is a protein selected from the group consisting of AP-1, Sp-1, rev, GCN4, λcro, λcI, TFIIA, myoD, retinoic acid receptor, glucocosteroid receptor, SV40 large T antigen, and GAL4 polypeptides.

12. The composition of either of claims 1, 2, or 8, wherein the nucleic binding domain is a polycation.

13. The composition of claim 12 wherein the polycation is selected from the group consisting of poly-L-lysine, protamine, histone and spermine.

14. The composition of claim 2 wherein the cytocide-encoding agent further comprises a tissue-specific promoter operably linked thereto.

15. The composition of claim 8 wherein the prodrug-encoding agent further comprises a tissue-specific promoter operably linked thereto.

16. The composition of either of claims 14 or 15 wherein the tissue-specific promoter is selected from the group consisting of alpha-crystalline promoter, tyrosinase promoter, α-fetoprotein promoter, prostate specific antigen promoter, CEA promoter, α-actin promoter, VEGF receptor promoter, erbB-2 promoter, C-myc promoter, cyclin D promoter, FGF receptor promoter and gamma-crystalline promoter.

17. The composition of claim 1, further comprising a tissue-specific promoter operably linked thereto.

18. The composition of claim 17 wherein the tissue specific promoter is a promoter selected from the group consisting of VEGF receptor promoter, tek promoter, tic promoter, urokinase receptor promoter, E-selectin promoter, P-selectin promoter, VCAM-1 promoter, endoglin promoter, endosialin promoter, alphav integrin promoter, β_3 integrin promoter, endothelin-1 promoter, ICAM-3 promoter, E9 promoter, von Willebrand Factor promoter, CD-44 promoter, CD40 promoter, vascular endothelial cadherin promoter, notch 4 promoter and high molecular weight melanoma-associated antigen promoter.

19. The composition of either of claims 1, 2, or 8, further comprising between one to six linkers that are selected from the group consisting of a cleavable linker, a linker that provides a sorting signal, a linker that reduces steric hindrance and a linker that contributes to a condensing ability of the nucleic acid binding domain, the addition of

said one to six linkers resulting in one of the following formulas: polypeptide that binds to an FGF receptor-L-nucleic acid binding domain-nucleic acid molecule, polypeptide that binds to an FGF receptor-L-nucleic acid binding domain-cytocide encoding agent, or the formula: polypeptide that binds to an FGF receptor-L-nucleic acid binding domain-prodrug encoding agent wherein: L is one to six linkers; and wherein the **conjugate** retains the ability to bind to an FGF receptor and internalize the nucleic acid molecule, cytocide-encoding agent or prodrug encoding agent, and wherein the cytocide-encoding agent is bound to the nucleic acid binding domain.

20. The composition of claim 19 wherein the linker is selected from the group consisting of a GlySer linker, a SerGly linker, or an AlaAlaProAla (SEQ ID NO: 51) linker.

21. The composition of claim 20, wherein the linker is encoded by a sequence selected from the group consisting of SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50.

22. The composition of claim 19 wherein the linker is a disulfide bond.

23. A method of delivering a nucleic acid molecule to a cell, comprising contacting a cell with the composition according to any one of claims 1 and 5-11, wherein the nucleic acid molecule is internalized in the cell.

24. A composition having the formula: polypeptide that binds to an fibroblast growth factor (FGF) receptor-nucleic acid molecule-nucleic acid binding domain, wherein: the nucleic acid molecule being **conjugated** to the polypeptide that binds to an FGF receptor; and wherein the nucleic acid molecule is bound to the nucleic acid binding domain; and wherein the composition binds to an FGF receptor and is internalized specifically in cells bearing the FGF receptor.

25. The composition of either of claims 1, 2, 8, or 24, wherein the polypeptide that binds to an FGF receptor is selected from the group consisting of an FGF-1 polypeptide, an FGF-2 polypeptide, an FGF-3 polypeptide, an FGF-4 polypeptide, an FGF-5 polypeptide, an FGF-6 polypeptide, an FGF-7 polypeptide, an FGF-8 polypeptide and an FGF-9 polypeptide.

26. The composition of either of claims 1, 2, 8, or 24, wherein the polypeptide that binds to an FGF receptor is an FGF-2 polypeptide.

27. The composition of claim 26, wherein FGF-2 of SEQ ID NO: 11 has a serine residue at position 96.

28. The composition of either of claims 1, 2, 8, or 24, wherein the polypeptide that binds to an FGF receptor is an FGF-7 polypeptide.

29. The composition of claim 19, wherein the polypeptide that binds to an FGF receptor is selected from the group consisting of an FGF-1 polypeptide, an FGF-2 polypeptide, an FGF-3 polypeptide, an FGF-4 polypeptide, an FGF-5 polypeptide, an FGF-6 polypeptide, an FGF-7 polypeptide, an FGF-8 polypeptide and an FGF-9 polypeptide.

30. The composition of claim 19, wherein the polypeptide that binds to an FGF receptor is an FGF-2 polypeptide.

31. The composition of claim 30, wherein FGF-2 of SEQ ID NO:11 has a serine residue at position 96.

32. The composition of claim 19, wherein the polypeptide that binds to

an FGF receptor is an FGF-7 polypeptide.

33. The composition of claim 19, wherein the cleavable linker is cleavable by a protease.

34. The composition of claim 33, wherein the protease is selected from the group consisting of cathepsin B, cathepsin D and trypsin.

35. The composition of claim 8, wherein the prodrug-encoding agent encodes HSV-thymidine kinase or cytosine deaminase.

L26 ANSWER 24 OF 25 USPATFULL on STN
2000:12922 Isolated peptides derived from **human immunodeficiency virus** types 1 and 2 containing fusion inhibitory domains.
Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6020459 20000201
APPLICATION: US 1995-484223 19950607 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An isolated peptide consisting of an amino acid sequence of a 16 to 39 amino acid residue region of an **HIV**-1 or **HIV**-2 retrovirus protein wherein said region is identified by an ALLMOTIS, 107x178x4, or PLZIP sequence search motif, and wherein said peptide is not a peptide with an amino acid sequence consisting of: (a) YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF (SEQ ID NO.1); (b) YTNTIYTLLEESQNQQEKNEQELLELDKWASLWNWF (SEQ ID NO.3); (c) YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNWF (SEQ ID NO.4); (d) YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF (SEQ ID NO.240); (e) NNLLRAIEAQQGLLQLTVWGIKQLQARILAVERYLKDQ (SEQ ID NO.241); (f) CGGNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ (SEQ ID NO.8); (g) NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQGGC (SEQ ID NO.242); (h) NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQGGC (SEQ ID NO.243); (i) CGGNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYKDQGGC (SEQ ID NO.244); or (j) LSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAV (SEQ ID NO.245), said peptide further consisting of an amino terminal X, and a carboxy terminal Z in which: X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

2. An isolated peptide having the formula: X-NKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO:210); X-SLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQ-Z (SEQ. ID. NO. 211); X-LEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQE-Z (SEQ. ID. NO. 212); X-EQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEK-Z (SEQ. ID. NO. 213); X-QIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKN-Z (SEQ. ID. NO. 214); X-IWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNE-Z (SEQ. ID. NO. 215); X-WNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQ-Z (SEQ. ID. NO. 216); X-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQE-Z (SEQ. ID. NO. 217); X-NMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQEL-Z (SEQ. ID. NO. 218); X-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-Z (SEQ. ID. NO. 219); X-TWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-Z (SEQ. ID. NO. 220); X-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-Z (SEQ. ID. NO. 221); X-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-Z SEQ. ID. NO. 222); X-WMEWDREINNYTSLIGSLIEESQNQQEKNEQELLE-Z (SEQ. ID. NO. 159); X-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-Z (SEQ. ID. NO. 223); X-EWDREINNYTSLIHSLIEESQNQQEKNEQELLELDK-Z (SEQ. ID. NO. 224);

X-WDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-Z (SEQ. ID. NO. 225);
X-DREINNYTSLIHSLIEESQNQQEKNEQELLELDKWA-Z (SEQ. ID. NO. 226);
X-REINNYTSLIHSLIEESQNQQEKNEQELLELDKWAS-Z (SEQ. ID. NO. 227);
X-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-Z (SEQ. ID. NO. 228);
X-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW-Z (SEQ. ID. NO. 229);
X-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-Z (SEQ. ID. NO. 230);
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-Z (SEQ. ID. NO. 185);
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWLIKFI-Z (SEQ. ID. NO. 160);
X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-Z (SEQ. ID. NO. 231);
X-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-Z (SEQ. ID. NO. 232);
X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWFNIT-Z (SEQ. ID. NO. 233);
X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 234);
X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 235);
X-ESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 236); X-NQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 237); X-EKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 238); X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNAF-Z (SEQ. ID. NO. 178); X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLANWF-Z (SEQ. ID. NO. 179);
X-YTSLIHSLIEESQNQQEKNEQQLLELDKWASLWNWF-Z (SEQ. ID. NO. 180);
X-YTSLIHSLIEESQNQQEKNEQELLQLDKWASLWNWF-Z (SEQ. ID. NO. 181);
X-YTSLIHSLIEESQNQQEKNQQELLQLDKWASLWNWF-Z (SEQ. ID. NO. 182);
X-YTSLIHSLQEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 183);
X-YTSLIHSLIEQSQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 186);
X-YTSLIHSLIQESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 187);
X-YTSLIHSLIEESQNQQEKNEQQLLELDKWASLWNWF-Z (SEQ. ID. NO. 190);
X-YTSLIQSLIEESQNQQEKNEQQLLELDKWASLWNWF-Z (SEQ. ID. NO. 191);
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLFNFF-Z (SEQ. ID. NO. 192);
X-YTSLIHSLIEESQNLQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 193);
X-YTSLIHSLIEESQNQQEKLEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 194);
X-YTSLIHSLIEESQNQQEKNEQELLEFDKWASLWNWF-Z (SEQ. ID. NO. 195);
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASPWNWF-Z (SEQ. ID. NO. 197); X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNSF-Z (SEQ. ID. NO. 198); or
X-LRAIEAQQHLLQLTVWQIKQLQARILAV-Z (SEQ. ID. NO. 239), in which: amino acid residues are presented by the single-letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

3. The peptide of claim 1 or 2 wherein group X is a hydrophobic group.

4. The peptide of claim 3 wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

5. The peptide of claim 1 or 2 wherein group Z is a hydrophobic group.

6. The peptide of claim 5 wherein the hydrophobic group Z is t-butyloxycarbonyl.

7. The peptide of claim 1 or 2 wherein group X is a macromolecular carrier group.

8. The peptide of claim 7 wherein the macromolecular carrier group is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

9. The peptide of claim 1 or 2 wherein the group Z is a macromolecular carrier group.

10. The peptide of claim 9 wherein the macromolecular carrier group Z is a lipid-fatty acid **conjugate**, a **polyethylene glycol**, or a carbohydrate moiety.

11. The peptide of claim 1 or 2 wherein at least one bond linking adjacent amino acid residues of the peptide is a non-peptide bond.

12. The peptide of claim 11 wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

13. The peptide of claim 1 or 2 wherein at least one amino acid residue of the peptide is in a D-isomer configuration.

14. The peptide of claim 1 or 2, wherein X is an acetyl group, and Z is an amido group.

15. The peptide of claim 2, wherein the peptide has the formula: X-NKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-Z (SEQ. ID. NO:210).

16. The peptide of claim 2, wherein the peptide has the formula: X-SLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQ-Z (SEQ. ID. NO. 211).

17. The peptide of claim 2, wherein the peptide has the formula: X-LEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQE-Z (SEQ. ID. NO. 212).

18. The peptide of claim 2, wherein the peptide has the formula: X-EQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEK-Z (SEQ. ID. NO. 213).

19. The peptide of claim 2, wherein the peptide has the formula: X-QIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKN-Z (SEQ. ID. NO. 214).

20. The peptide of claim 2, wherein the peptide has the formula: X-IWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNE-Z (SEQ. ID. NO. 215).

21. The peptide of claim 2, wherein the peptide has the formula: X-WNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQ-Z (SEQ. ID. NO. 216).

22. The peptide of claim 2, wherein the peptide has the formula: X-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQE-Z (SEQ. ID. NO. 217).

23. The peptide of claim 2, wherein the peptide has the formula: X-NMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQEL-Z (SEQ. ID. NO. 218).

24. The peptide of claim 2, wherein the peptide has the formula: X-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-Z (SEQ. ID. NO. 219).

25. The peptide of claim 2, wherein the peptide has the formula: X-TWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-Z (SEQ. ID. NO. 220).

26. The peptide of claim 2, wherein the peptide has the formula: X-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-Z (SEQ. ID. NO. 221).

27. The peptide of claim 2, wherein the peptide has the formula: X-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-Z (SEQ. ID. NO. 222).

28. The peptide of claim 2, wherein the peptide has the formula: X-WMEWDREINNYTSLIGSLIEESQNQQEKNEQELLE-Z (SEQ. ID. NO. 159).

29. The peptide of claim 2, wherein the peptide has the formula: X-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-Z (SEQ. ID. NO. 223).

30. The peptide of claim 2, wherein the peptide has the formula: X-EWDREINNYTSLIHSLIEESQNQQEKNEQELLELDK-Z (SEQ. ID. NO. 224).

31. The peptide of claim 2, wherein the peptide has the formula:

X-WDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-Z (SEQ. ID. NO. 225).

32. The peptide of claim 2, wherein the peptide has the formula:
X-DREINNYTSLIHSLIEESQNQQEKNEQELLELDKWA-Z (SEQ. ID. NO. 226).

33. The peptide of claim 2, wherein the peptide has the formula:
X-REINNYTSLIHSLIEESQNQQEKNEQELLELDKWAS-Z (SEQ. ID. NO. 227).

34. The peptide of claim 2, wherein the peptide has the formula:
X-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-Z (SEQ. ID. NO. 228).

35. The peptide of claim 2, wherein the peptide has the formula:
X-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW-Z (SEQ. ID. NO. 229).

36. The peptide of claim 2, wherein the peptide has the formula:
X-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-Z (SEQ. ID. NO. 230).

37. The peptide of claim 2, wherein the peptide has the formula:
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-Z (SEQ. ID. NO. 185).

38. The peptide of claim 2, wherein the peptide has the formula:
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWLIKFI-Z (SEQ. ID. NO. 160).

39. The peptide of claim 2, wherein the peptide has the formula:
X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-Z (SEQ. ID. NO. 231).

40. The peptide of claim 2, wherein the peptide has the formula:
X-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-Z (SEQ. ID. NO. 232).

41. The peptide of claim 2, wherein the peptide has the formula:
X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWFNIT-Z (SEQ. ID. NO. 233).

42. The peptide of claim 2, wherein the peptide has the formula:
X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 234).

43. The peptide of claim 2, wherein the peptide has the formula:
X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 235).

44. The peptide of claim 2, wherein the peptide has the formula:
X-ESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 236).

45. The peptide of claim 2, wherein the peptide has the formula:
X-NQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 237).

46. The peptide of claim 2, wherein the peptide has the formula:
X-EKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 238).

47. The peptide of claim 2, wherein the peptide has the formula:
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNAF-Z (SEQ. ID. NO. 178).

48. The peptide of claim 2, wherein the peptide has the formula:
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLANWF-Z (SEQ. ID. NO. 179).

49. The peptide of claim 2, wherein the peptide has the formula:
X-YTSLIHSLIEESQNQQEKNEQQLLELDKWASLWNWF-Z (SEQ. ID. NO. 180).

50. The peptide of claim 2, wherein the peptide has the formula:
X-YTSLIHSLIEESQNQQEKNEQELLQLDKWASLWNWF-Z (SEQ. ID. NO. 181).

51. The peptide of claim 2, wherein the peptide has the formula:
X-YTSLIHSLIEESQNQQEKNQQELLQLDKWASLWNWF-Z (SEQ. ID. NO. 182).

52. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLQEESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 183).

53. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIEQSQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 186).

54. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIQESQNQQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 187).

55. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIEESQNQQEKNEQQLLELDKWASLWNWF-Z (SEQ. ID. NO. 190).

56. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIQSLIEESQNQQEKNEQQLLELDKWASLWNWF-Z (SEQ. ID. NO. 191).

57. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLFNFF-Z (SEQ. ID. NO. 192).

58. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIEESQNLQEKNEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 193).

59. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIEESQNQQEKLEQELLELDKWASLWNWF-Z (SEQ. ID. NO. 194).

60. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIEESQNQQEKNEQELLEFDKWASLWNWF-Z (SEQ. ID. NO. 195).

61. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASPWNWF-Z (SEQ. ID. NO. 197).

62. The peptide of claim 2, wherein the peptide has the formula: X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNSF-Z (SEQ. ID. NO. 198).

63. The peptide of claim 2, wherein the peptide has the formula: X-LRAIEAQQHLLQLTVWQIKQLQARILAV-Z (SEQ. ID. NO. 239).

64. The peptide of any one of claims 15 through 63, wherein X is an acetyl group, and Z is an amido group.

65. The peptide of claim 1, wherein the region of the **HIV**-1 or **HIV**-2 retrovirus protein is a region of 28 amino acid residues identified by the ALLMOTI5 motif.

66. The peptide of claim 1, wherein the region of the **HIV**-1 or **HIV**-2 retrovirus protein is a region of 35 amino acid residues identified by the ALLMOTI5 motif.

67. The peptide of claim 1, wherein the region of the **HIV**-1 or **HIV**-2 retrovirus protein is a region of 28 amino acid residues identified by the 107x178x4 motif.

68. The peptide of claim 1, wherein the region of the **HIV**-1 or **HIV**-2 retrovirus protein is a region of 35 amino acid residues identified by the 107x178x4 motif.

69. The peptide of claim 1, wherein the region of the **HIV**-1 or **HIV**-2 retrovirus protein is identified by the PLZIP motif.

70. The peptide of claim 7, wherein the macromolecular group is a peptide group.

71. The peptide of claim 70, wherein the peptide group is about 2 to

about 50 amino acid residues amino to the **HIV**-1 or **HIV**-2 protein identified by an ALLMOITI5, 107x178x4 or PLZIP sequence search motif.

72. The peptide of claim 9, wherein the macromolecular group is a peptide group.

73. The peptide of claim 72, wherein the peptide group is about 2 to about 50 amino acid residues carboxy to the **HIV**-1 or **HIV**-2 protein identified by an ALLMOTI5, 107x178x4 or PLZIP sequence search motif.

74. The peptide of claim 73, wherein the group X is a peptide group.

75. The peptide of claim 74, wherein the peptide group X is about 2 to about 50 amino acid residues amino to the **HIV**-1 or **HIV**-2 protein identified by an ALLMOTI5, 107x178x4 or PLZIP sequence search motif.

L26 ANSWER 25 OF 25 USPATFULL on STN
2000:4427 Measles virus peptides with antifusogenic and antiviral activities.
Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6013263 20000111
APPLICATION: US 1995-486099 19950607 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An isolated peptide consisting of an amino acid sequence of a 16 to 39 amino acid residue region of a measles virus protein, wherein said region comprises an amino acid sequence identified by an ALLMOTI5, 107x178x4, or PLZIP sequence search motif, said peptide further consisting of an amino terminal X, and a carboxy terminal Z in which: X comprises an amino group an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

2. A peptide having the formula X-LHRIDLGPPISLERLDVGTNLGNAIAKLEDAKELL-Z (SEQ ID NO: 73),
X-HRIDLGPPISLERLDVGTNLGNAIAKLEDAKELLE-Z (SEQ ID NO: 74),
X-RIDLGPPISLERLDVGTNLGNAIAKLEDAKELLES-Z (SEQ ID NO: 75),
X-IDLGPPISLERLDVGTNLGNAIAKLEDAKELLESS-Z (SEQ ID NO: 76),
X-DLGPPISLERLDVGTNLGNAIAKLEDAKELLESSD-Z (SEQ ID NO: 77),
X-LGPPISLERLDVGTNLGNAIAKLEDAKELLESSDQ-Z (SEQ ID NO: 78),
X-GPPISLERLDVGTNLGNAIAKLEDAKELLESSDQI-Z (SEQ ID NO: 79),
X-PPISLERLDVGTNLGNAIAKLEDAKELLESSDQIL-Z (SEQ ID NO: 80),
X-PISLERLDVGTNLGNAIAKLEDAKELLESSDQILR-Z (SEQ ID NO: 81),
X-SLERLDVGTNLGNAIAKLEDAKELLESSDQILRSM-Z (SEQ ID NO: 82),

or
- X-LERLDVGTNLGNAIAKLEDAKELLESSDQILRSMK-Z (SEQ ID NO: 83),

in which amino acid residues are presented by the single letter code; X comprises an amino group, an acetyl group, a 9-fluorenylmethoxy-carbonyl group, a hydrophobic group, or a macromolecular carrier group; and Z comprises a carboxyl group, an amido group, a hydrophobic group, or a macromolecular carrier group.

3. The peptide of claim 1 or 2, wherein X is an acetyl group, and Z is an amido group.

4. The peptide of claim 2, wherein the peptide has the formula X-LHRIDLGPPISLERLDVGTNLGNAIAKLEDAKELL-Z (SEQ ID NO:73).

5. The peptide of claim 2, wherein the peptide has the formula X-HRIDLGPPISLERLDVGTNLGNAIAKLEDAKELLE-Z (SEQ ID NO:74).

6. The peptide of claim 2, wherein the peptide has the formula X-RIDLGPPISLERLDVGTNLGNAIAKLEDAKELLES-Z (SEQ ID NO:75).

7. The peptide of claim 2, wherein the peptide has the formula X-IDLGPPISLERLDVGTNLGNAIAKLEDAKELLESS-Z (SEQ ID NO:76).

8. The peptide of claim 2, wherein the peptide has the formula X-DLGPPISLERLDVGTNLGNAIAKLEDAKELLESSD-Z (SEQ ID NO:77).

9. The peptide of claim 2, wherein the peptide has the formula X-LGPPISLERLDVGTNLGNAIAKLEDAKELLESSDQ-Z (SEQ ID NO:78).

10. The peptide of claim 2, wherein the peptide has the formula X-GPPISLERLDVGTNLGNAIAKLEDAKELLESSDQI-Z (SEQ ID NO:79).

11. The peptide of claim 2, wherein the peptide has the formula X-PPISLERLDVGTNLGNAIAKLEDAKELLESSDQIL-Z (SEQ ID NO:80).

12. The peptide of claim 2, wherein the peptide has the formula X-PISLERLDVGTNLGNAIAKLEDAKELLESSDQILR-Z (SEQ ID NO:81).

13. The peptide of claim 2, wherein the peptide has the formula X-SLERLDVGTNLGNAIAKLEDAKELLESSDQILRSM-Z (SEQ ID NO:82).

14. The peptide of claim 2, wherein the peptide has the formula X-LERLDVGTNLGNAIAKLEDAKELLESSDQILRSMK-Z (SEQ ID NO:83).

15. The peptide of claim 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14, wherein X is an acetyl group, and Z is an amido group.

16. The peptide of claim 1 or 2 wherein group X is a hydrophobic group.

17. The peptide of claim 16 wherein the hydrophobic group X is carbobenzoxyl, dansyl, or t-butyloxycarbonyl.

18. The peptide of claim 1 or 2 wherein group Z is a hydrophobic group.

19. The peptide of claim 18 wherein the hydrophobic group Z is t-butyloxycarbonyl.

20. The peptide of claim 1 or 2 wherein group X is a macromolecular carrier group.

21. The peptide of claim 20 wherein the macromolecular carrier group is

a lipid-fatty acid conjugate, a polyethylene glycol, or a carbohydrate moiety.

22. The peptide of claim 1 or 2 wherein the group Z is a macromolecular carrier group.

23. The peptide of claim 22 wherein the macromolecular carrier group Z is a lipid-fatty acid conjugae, a polyethylene glycol, or a carbohydrate moiety.

24. The peptide of claim 1 or 2 wherein at least one bond linking adjacent amino acid residues of the peptide is a non-peptide bond.

25. The peptide of claim 24 wherein the non-peptide bond is an imino, ester, hydrazine, semicarbazide, or azo bond.

26. The peptide of claim 1 or 2 wherein at least one amino acid residue of the peptide is in a D-isomer configuration.

27. The peptide of claim 1 or 2, wherein X is an acetyl group, and Z is an amido group.

28. The peptide of claim 1, wherein the region of the measles virus protein is a region of 28 amino acid residues identified by the ALLMOTI5 motif.

29. The peptide of claim 1, wherein the region of the measles virus protein is a region of 35 amino acid residues identified by the ALLMOTI5 motif.

30. The peptide of claim 1, wherein the region of the measles virus protein is a region of 28 amino acid residues identified by the 107x178x4 motif.

31. The peptide of claim 1, wherein the region of the measles protein is a region of 35 amino acid residues identified by the 107x178x4 motif.

32. The peptide of claim 1, wherein the region of the measles virus protein is identified by the PLZIP motif.

33. The peptide of claim 20, wherein the macromolecular group is a peptide group.

34. The peptide of claim 33, wherein the peptide group is about 2 to about 50 amino acid residues amino to the measles virus protein identified by an ALLMOITI5, 107x178x4 or PLZIP sequence search motif.

35. The peptide of claim 22, wherein the macromolecular group is a peptide group.

36. The peptide of claim 35, wherein the peptide group is about 2 to about 50 amino acid residues carboxy to the measles virus protein identified by an ALLMOTI5, 107x178x4 or PLZIP sequence search motif.

37. The peptide of claim 36, wherein the group X is a peptide group.

38. The peptide of claim 37, wherein the peptide group X is about 2 to about 50 amino acid residues amino to the measles virus protein identified by ALLMOTI5, 107x178x4 or PLZIP sequence search motif.

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=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    54.29     120.99

FILE 'MEDLINE' ENTERED AT 05:27:32 ON 02 OCT 2006

 FILE LAST UPDATED: 30 Sep 2006 (20060930/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s (HIV or human immunodeficiency virus)
        163348 HIV
       1420903 HUMAN
        124822 IMMUNODEFICIENCY
        419508 VIRUS
         49412 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L27     168740 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

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           202 HR2
           949 HEPTAD
L28        161 L27 AND (HR1 OR HR2 OR HEPTAD)

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         82786 CONJUGAT?
L29          4 L28 AND CONJUGAT?

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L29  ANSWER 1 OF 4     MEDLINE on STN
2004415436.    PubMed ID: 15320988.   An inducible HIV type 1 gp41 HR-2
     peptide-binding site on HIV type 1 envelope gp120. Alam S Munir; Paleos
     Casey A; Liao Hua-Xin; Scearce Richard; Robinson James; Haynes Barton F.
     (Department of Medicine, Duke Center for AIDS Research, Human Vaccine
     Institute, Duke University School of Medicine, Durham, North Carolina
     27707, USA. ) AIDS research and human retroviruses, (2004 Aug) Vol. 20,
     No. 8, pp. 836-45.  Journal code: 8709376. ISSN: 0889-2229. Pub. country:
     United States. Language: English.
AB   Synthetic peptides of sequences within the HIV-1 gp41 heptad
     repeat-regions (HR-1 and HR-2) can effectively inhibit cell fusion and
     viral entry.  DP178 (T-20), an HR-2 peptide, acts by inhibiting the
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association between HR-1 and HR-2, thereby interfering with **HIV**-1 fusion and viral entry. HR-2 peptide binding is predicted to be an important indicator of the presence of Env gp41 fusion intermediate conformation. A stabilized HR-2/Env **conjugate** might be an **HIV**-1 vaccine candidate and have the potential for inducing antibodies against transiently exposed epitopes on **HIV**-1 Env. To explore the possibility of design of HR-2 stabilized-**HIV**-1 immunogens, we studied the ability of **HIV**-1 Env to bind to HR-2 peptides. Using surface plasmon resonance (SPR)-binding assays and precipitation of soluble Env gp120 proteins with HR-2 peptide DP178, we have found that there is an HR-2 peptide-binding site on soluble **HIV**-1 recombinant gp120. Binding of DP178 was induced by sCD4 and by the anti-gp120 human mAb A32. The induction of DP178 binding was inhibited > 80% by the **HIV**-1 coreceptor-binding site mAb 17b. Binding of DP178 to gp120 was also inhibited by gp120 C4 peptides with sequences that are centrally located within the **HIV**-1 coreceptor-binding site. Thus, in addition to interactions with the gp41 HR-1 region, the fusion inhibitor peptide DP178 binds to triggered soluble **HIV**-1 recombinant gp120 following its interaction with sCD4 or CD4 mimic mAb A32. This may prove to be an important consideration when designing an **HIV** vaccine that utilizes constrained **HIV** Env proteins.

L29 ANSWER 2 OF 4 MEDLINE on STN

2004014811. PubMed ID: 14711394. Rapid and automated fluorescence-linked immunosorbent assay for high-throughput screening of **HIV**-1 fusion inhibitors targeting gp41. Liu Shuwen; Boyer-Chatenet Louise; Lu Hong; Jiang Shibo. (Lindsley F. Kimball Research Institute, New York Blood Center, New York, NY 10021, USA.) Journal of biomolecular screening : the official journal of the Society for Biomolecular Screening, (2003 Dec) Vol. 8, No. 6, pp. 685-93. Journal code: 9612112. ISSN: 1087-0571. Pub. country: United States. Language: English.

AB The **human immunodeficiency virus** type 1 (**HIV**-1) envelope glycoprotein gp41 plays an important role in the virus entry. During the process of fusion between the viral and target cell membranes, the N- and C-terminal **heptad** repeat (HR) regions of the gp41 extracellular domain associate to form a 6-helical bundle, corresponding to the fusion-active gp41 core. Any compound that blocks the gp41 6-helix bundle formation between the N- and C-peptides, which are derived from the N- and C-terminal HR regions, respectively, may inhibit **HIV**-1 mediated membrane fusion. Based on this principle, we previously established a sandwich enzyme-linked immunosorbent assay (ELISA) for drug screening by using the N-peptide N36 and the C-peptide C34 and a monoclonal antibody (NC-1) which specifically recognizes the gp41 6-helix bundle. In the present study, a fluorescence-linked immunosorbent assay (FLISA) was developed by using fluorescein isothiocyanate (FITC)-**conjugated** C34 to replace C34 and by directly detecting fluorescence intensity instead of more complicated enzymatic reaction. Compared with the sandwich ELISA, this FLISA has similar sensitivity and specificity, but it is much more rapid, economic and convenient. Using an Integrated Robotic Sample Processing System, this assay has been applied for high-throughput screening of organic compounds on a large scale for **HIV**-1 fusion inhibitors targeting gp41.

L29 ANSWER 3 OF 4 MEDLINE on STN

2003565061. PubMed ID: 14651977. Mutations in gp41 and gp120 of **HIV**-1 isolates resistant to hexa-arginine neomycin B **conjugate**. Borkow Gadi; Lara Humberto Herman; Lapidot Aviva. (Department of Organic Chemistry, The Weizmann Institute of Science, 76100, Rehovot, Israel.) Biochemical and biophysical research communications, (2003 Dec 26) Vol. 312, No. 4, pp. 1047-52. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Aminoglycoside-arginine **conjugates** (AACs) inhibit **HIV**-1 replication and act as Tat antagonists. AACs compete with monoclonal antibody binding to CXCR4, compete with SDF-1alpha and **HIV**-1 gp120 cellular uptake,

indicating that they interfere with initial steps of **HIV**-1 infection. We here present the selection of **HIV**-1 isolates resistant to hexa-arginine neomycin B **conjugate** (NeoR6), the most potent anti-**HIV**-1 AAC. We found in the NeoR6-resistant isolates the following mutations in gp120: I339T in the C3 region, S372L in the V4 region, and Q395K in the C4 region; and in gp41: S668R and F672Y in the '**heptad** repeat' 2 (**HR2**) region. These findings strongly suggest that NeoR6 obstructs **HIV**-1 replication by interfering with the fusion step, dependent on both conformational changes in gp120 following CD4 and CXCR4 interaction, as well as by conformational changes in gp41 induced by **HR1** and **HR2** interaction. The AACs may thus represent a novel family of fusion inhibitors.

L29 ANSWER 4 OF 4 MEDLINE on STN

2002688156. PubMed ID: 12237296. Enhancement of alpha -helicity in the **HIV**-1 inhibitory peptide DP178 leads to an increased affinity for human monoclonal antibody 2F5 but does not elicit neutralizing responses in vitro. Implications for vaccine design. Joyce Joseph G; Hurni William M; Bogusky Michael J; Garsky Victor M; Liang Xiaoping; Citron Michael P; Danzeisen Renee C; Miller Michael D; Shiver John W; Keller Paul M. (Department of Virus and Cell Biology, Merck Research Laboratories, West Point, Pennsylvania 19486, USA.. joseph_joyce@merck.com) . The Journal of biological chemistry, (2002 Nov 29) Vol. 277, No. 48, pp. 45811-20. Electronic Publication: 2002-09-16. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The synthetic peptide DP178, derived from the carboxyl-terminal **heptad** repeat region of **human immunodeficiency virus** type 1 GP41 protein is a potent inhibitor of viral-mediated fusion and contains the sequence ELDKWA, which constitutes the recognition epitope for the broadly neutralizing human monoclonal antibody 2F5. Efforts at eliciting a 2F5-like immune response by immunization with peptides or fusion proteins containing this sequence have not met with success, possibly because of incorrect structural presentation of the epitope. Although the structure of the carboxyl-terminal **heptad** repeat on the virion is not known, several recent reports have suggested a propensity for alpha-helical conformation. We have examined DP178 in the context of a model for optimized alpha-helices and show that the native sequence conforms poorly to the model. Solution conformation of DP178 was studied by circular dichroism and NMR spectroscopy and found to be predominantly random, consistent with previous reports. NMR mapping was used to show that the low percentage of alpha-helix present was localized to residues Glu(662) through Asn(671), a region encompassing the 2F5 epitope. Using NH(2)-terminal extensions derived from either GP41 or the yeast GCN4 leucine zipper dimerization domain, we designed peptide analogs in which the average helicity is significantly increased compared with DP178 and show that these peptides exhibit both a modest increase in affinity for 2F5 using a novel competitive solution-based binding assay and an increased ability to inhibit viral entry in a single-cycle infectivity model. Selected peptides were **conjugated** to carrier protein and used for guinea pig immunizations. High peptide-specific titers were achieved using these immunogens, but the resulting sera were incapable of viral neutralization. We discuss these findings in terms of structural and immunological considerations as to the utility of a 2F5-like response.

=> d his

(FILE 'HOME' ENTERED AT 05:19:18 ON 02 OCT 2006)

FILE 'USPATFULL' ENTERED AT 05:19:28 ON 02 OCT 2006
E BRAY BRIAN/IN
L1 13 S E3-E5

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L2              6 S L1 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3              6 S L2 AND (CONJUGATE? OR HR1 OR HR2 OR HEPTAD)
                  E KANG MYUNG CHOI/IN
L4              5 S E4
L5              0 S L4 NOT L1
                  E TVERMOES NICOLAI/IN
L6              3 S E3-E4
L7              2 S L6 NOT L1
                  E KINDER DANIEL/IN
L8              5 S E3-E5
L9              4 S L8 NOT L1
                  E LACKEY JOHN W/IN
L10            10 S E3 OR E4
L11             5 S L10 AND (CONJUGAT? OR HEPTAD OR HR1 OR HR2)

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L12             8 S E3
L13             4 S L12 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)
                  E LACKEY J W/IN
L14             9 S E3
L15             8 S L14 NOT L13
L16             0 S L15 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)

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                  E BRAY B/AU
L18            15 S E3
L19             0 S L18 AND (CONJUGAT? OR HR1 OR HR2 OR HEPTAD)
                  E LACKEY J W/AU

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L20         47774 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21           537 S L20 AND (HR1 OR HR2 OR HEPTAD)
L22           439 S L21 AND CONJUGAT?
L23           305 S L22 AND (PEG? OR POLYETHYLENE GLYCOL)
L24            29 S L23 AND (CONJUGAT?/CLM)
L25            28 S L24 NOT L1
L26            25 S L25 AND AY<2004

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L27        168740 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L28           161 S L27 AND (HR1 OR HR2 OR HEPTAD)
L29             4 S L28 AND CONJUGAT?

=> log off
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 05:28:11 ON 02 OCT 2006
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